Applications of Morita-Baylis-Hillman Reaction to the Synthesis of Natural Products and Drug Molecules

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Abstract: The synthesis of complex natural products from simple and common intermediates has been one of the major goals in synthetic organic chemistry. Toward this objective, if such simple scaffolds are suitably decorated with diverse functional groups they present opportunities not only to synthesize the target compounds but also construct the close analogues to investigate the biological properties. The Morita-Baylis-Hillman (MBH) reaction is an organocatalyzed C-C bond forming reaction that leads to multifunctional products thereby offering viable alternatives for employing them for other complexity generating reactions. This property has been extensively utilized for the synthesis of natural products of microbial, animal, terrestrial, and marine origins. Simultaneously, MBH adducts are precursors to several drug molecules or their intermediates. This comprehensive review assimilates applications of the Morita-Baylis-Hillman reaction for the synthesis of different natural products and drug molecules.

Keywords: Alkaloid, Drugs, Marine, Morita-Baylis-Hillman, Natural Product, Terpenoid.

1. INTRODUCTION

The Morita-Baylis-Hillman (MBH) reaction is considered to be a unique complexity generating organocatalytic reaction between an activated alkene and carbonyl electrophiles under the influence of a nucleophilic species providing a simple and convenient method for the synthesis of densely functionalized products (Fig. 1). First reported in 1968 by Morita [1] as carbinol addition reaction followed by patents from Baylis and Hillman in 1972 [2], this reaction has grown exponentially especially during the last two decades and has now become a standard method in the toolbox of the synthetic organic chemists. Some of the hallmarks of this C-C bond forming reaction, which is generally performed using cheap and commercially available starting reagents, include atom-economy, ease of execution and chemospecific groups in the product for further synthetic diversifications. At least four different chemical groups (D-1 to D-4, Fig. 1) in the MBH adduct allow construction of diverse units in the realms of heterocyclic and natural product chemistry.

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{mbh_react.png}
\caption{MBH reaction displaying the 4-chemospecific groups in the adduct.}
\end{figure}

The growth of the reaction gained momentum after a review of the literature encompassing the scope of the reaction and its application by Basavaiah et al. published in 1996 [3]. Another comprehensive review from Basavaiah’s group in 2003 further catalyzed the progress of this reaction [4]. Subsequently, several groups joined into exploring the utility of adduct for many objectives and the progress made was assimilated in the form of reviews or mini-reviews [5]. During the course of our studies related to exploration of the MBH chemistry, we realized that despite several reviews on the development of this reaction, there is no dedicated review on applications of the MBH reaction in synthesis of natural products and drugs or drug intermediates. Although the 5\textsuperscript{th} chapter of the book edited by Shi includes the information related to the impact of MBH chemistry in the natural product chemistry, it has limited availability [6]. In 2012, Lima and Vasconcellos reviewed the several derivatives generated employing the MBH chemistry which were demonstrated to show different pharmacological activities but the impact of this reaction on obtaining drug or drug intermediates was not covered in this review [7]. This prompted us to write a comprehensive review concerning the use of the MBH reaction for the syntheses of natural products and drugs or drug intermediates. The search of literature for this review was performed using SciFinder. This review covers all citations describing the use of MBH
reaction at any of the step during the synthesis of the target natural product or drug intermediate till February 2014. However the synthesis of natural product mimics using MBH chemistry is beyond the scope of this article. The schemes included in this review necessarily delineate the MBH reaction step but may not essentially outline each step before or after the MBH reaction employed in the series to reach to the target molecule. Since the mechanistic details of the MBH reaction are discussed extensively in the published reviews and there is no significant development on this aspect in recent past, we are excluding it from the scope of this article. The contents of the review are arranged on the basis of the source of the natural products from where it was isolated followed by the synthesis of drug molecules.

2. SYNTHESIS OF NATURAL PRODUCTS OF MICROBIAL ORIGIN

Microorganisms such as bacteria and fungi are considered as precious sources for discovering natural compounds with diverse bioactivities. The screening of compounds of microbial origin has resulted into the discovery of an arsenal of antibiotics including penicillin, chloramphenicol, cephalosporin etc. and has also served as viable alternative for obtaining lead molecules for many other diseases. In the first section citations pertaining to the synthesis of bioactive natural products of microbial origin involving MBH reaction as the key step are presented.

2.1. Natural Products of Bacterial Origin

2.1.1. Phosphonothrixin

Fields used the MBH adduct of acetaldehyde for the synthesis of phosphonothrixin (7) [8], a phosphorous containing herbicidal natural product, isolated from Saccharothrix sp. ST-888 [9]. The phosphorylation of the MBH adduct (2) [10] of acetaldehyde with diethyl chlorophosphite led to a product which upon heating at 80 °C underwent Arbuzov reaction to afford E-allyl phosphate 3 in 60% yield (Scheme 1). Reduction of the ester in 3 gave the primary alcohol 4. Silyl ether protection followed by vicinal dihydroxylation with OsO₄ gave 5 which upon selective oxidation of the secondary hydroxyl group furnished the protected phosphonothrixin 7. Deprotecting all the functional groups afforded the salt free protonated phosphonothrixin 1.

2.1.2. Pentenomycin

(-)-Pentenomycin 1 (16), a cyclopentenoid natural product with antibacterial activity against both Gram-positive and Gram-negative bacterial strains was isolated from the culture filtrate of Streptomyces eurythermus [11]. Sugahara and Ogasawara developed a novel route for the synthesis of this natural antibiotic by carrying out MBH reaction of formaldehyde with a chiral ketodicyclopentadiene (8) to prepare the adduct 9 [12]. Reducing the keto group in 9 with DIBAL-H afforded the endo-allyl alcohol 10 which was then exposed to NBS to dibrominate the double bond and subsequently dehydrobrominated to block one of the olefins regioselectively leading to 11. A series of reactions on 11 led to 14 from which the enone double bond of pentenomycin was regenerated via thermolysis in diphenyl ether at 280 °C to obtain 15. The acid-mediated deprotection of acetonide and MOM group in 15 afforded (-)-pentenomycin 1 (16) in enantiomerically pure form (Scheme 2).

2.1.3. Epopromycin B

Epopromycin B (25), a novel plant cell wall synthesis inhibitor was isolated from the culture broth of Streptomyces sp. NK04000 [13]. Hatakeyama and co-workers developed an enantio- and diastereo-controlled route to the synthesis of epopromycin B and 2-epi-epopromycin B (28) using β-LCD-catalyzed MBH reaction as one of the key steps [14]. The synthesis was initiated with the MBH reaction of (S)-N-Fmoc-leucinal with HFIPA to afford a mixture of 18 and 19 which upon methanolysis by NaOMe afforded methyl esters 20 and 21, respectively (Scheme 3). However, performing an identical MBH reaction with (R)-N-Fmoc leucinal failed to afford the product. Subsequently the adduct 20 was subjected to epoxidation under two different conditions to afford the precursor 24 and 27 for epopromycin B and 2-epi-epopromycin B [15], respectively.

2.1.4. Acaterin

(-)-Acaterin (31), a secondary metabolite having 2-penten-4-olide structure, was isolated from Pseudomonas sp. [16]. It is an acetyl-CoA-cholesterol acyltransferase inhibitor and is projected to be effective in the treatment of diseases like atherosclerosis and hypercholesterolemia. The MBH adduct 31, generated from a reaction between α,β-unsaturated γ-lactone (29) and octanal (30), was used by Frank and Figadère to accomplish the synthesis of racemic acaterin (31) (Scheme 4) [17]. During optimization studies for the MBH reaction, they discovered that the best yields of 31 was obtained when the reaction was performed in dioxane:water in the presence of Mg(ClO₄)₂ as additive. They discovered that irrespective of use of chiral or achiral lactone only the racemic products were isolated.
Scheme 2.

Scheme 3.

Scheme 4.
protected acaterin (31) and its diastereomer (41) starting from MBH adduct 35 (Scheme 5) [18]. A quinuclidine-mediated MBH reaction of caprylic aldehyde 34 with methyl acrylate gave the adduct 35.  

Protecting the hydroxyl group in 35 as methoxymethoxymethyl ether, followed by saponification and coupling with R-(-)-3-butene-2-ol gave the diallyl derivatives 39 and 40 as mixture of diastereomers. Ring closing metathesis and separation of the product gave the diallyl derivatives 39 and 40 which allowed them to access chloramphenicol (51) [20]. A TiCl₄-mediated de-protection of 39 gave the natural (-)-acaterin (31) whereas 40 afforded the other diastereomer 41.

2.1.5. Chloramphenicol

Chloramphenicol (51) is the first example of an antibiotic discovered through screening of soil microorganisms and is also the only example of this class of compounds which was commercialized for therapeutics [19]. Coelho and Rossi developed a straightforward and diastereoselective route to functionalized oxazolidines starting from the MBH adduct (43) of piperonal (Scheme 6) [20]. The protocol involved initial transformation of the MBH adducts into diol which was further extended to obtain the oxazolidines 48. Such oxazolidines were earlier reported to cleave to afford the chloramphenicol [21].

1. TPAP, NMO, CH₂Cl₂, MS 4 Å, 15 min, rt, 98%
2. NaClO₃, NaH₂PO₄, b-ButOH, H₂O, 2-methyl-but-2-ene, rt, 14 h, 90%

Subsequently Mateus and Coelho developed an alternate route for the synthesis of amine diols starting from the MBH adducts which allowed them to access chloramphenicol (51), fluoramphenicol (58) and thiamphenicol (59) stereoselectively [22]. Their strategy involved the preparation of ene carbamate from the MBH adduct 54, 55 via a Curtius rearrangement followed by stereoselective hydroboration to obtain the intermediate 2-amino-1,3-diols 56 or 57, respectively (Scheme 7). These intermediates were directly transformed into the title antibiotics.

2.1.6. Furaquinocine

The furaquinocins class of antibiotics, isolated from the fermentation broth of Streptomyces sp. [23] show a wide range of biological activities which include in vitro cytotoxicity against HeLa S3 and B16 melanoma cells, antihypertensive activity, and inhibition of platelet aggregation and coagulation. All members of the furaquinocins possess a densely functionalized naphthoquinone core. Based on DYKAT process, Trost et al. developed the total synthesis of furaquinocin E (67) from the MBH derivative 62 (Scheme 8) which was prepared from the MBH adduct 60 [24, 25]. They elegantly extended the scope of their strategy by developing the synthesis of furaquinocin A (68) and B (69) and three more
Scheme 7.

Scheme 8.
analogue of furauquinocin E [26], thereby demonstrating the modular property of the strategy. Dialkylation of 2-iodoresorcinol with the allylic carbamate (62) prepared from the MBH adduct gave 63 in excellent yield and high stereoselectivity. Heck reaction in the presence of a sterically hindered base pentamethyl piperidine (PMP) followed by acetalization gave the acetate 64. Saponification of the acetate 64, TIPS protection of the free phenol followed by regioselective bromination of the phenyl ring afforded compound 65. Reduction of the nitrile group to the formyl group by HWE reaction gave the diene 66 which was transformed into the required furauquinocin E in 4 steps. A squaric acid-based methodology for generating napthaquinone was utilized for the process.

2.1.7. Spinosyn A

Spinosyn A (78), a polyketide natural product is the main component of a biosynthetic mixture produced by the soil microbe Saccharopolyspora spinosa [27]. Because of its low toxicity to beneficial insects and quick degradation in the environment Dow AgroSciences marketed it as an agricultural insecticide against a variety of insects. Roush et al. developed a PMe₂-catalyzed tandem intramolecular Diels-Alder reaction and vinylogous MBH reaction (also known as Rauhut-Currier reaction) to obtain the tricyclic core of (-)-spinosyn A with five defined stereo centres (Scheme 9) [28]. They showed that the olefin geometry in 71 had a critical effect on the product distribution in the phosphine-catalyzed cyclization of enone-enoate. The (Z)-enoate 71 afforded the desired product 72 in excellent chemoselectivity (96:4) while with the (E)-enoate the selectivity is less (2:1). It was presumed that the (Z)-enoate restricted orbital alignment and therefore suppressed γ-deprotonation, required for the formation of olefin migration by-product 73.

Subsequently they extended this protocol to achieve the total synthesis of both (-)-spinosyn A aglycon (78) and (-)-spinosyn A pseudoaglycon (76) (Scheme 10) [29].

2.1.8. FR182877

FR182877, an antimitotic agent which was isolated by Fujisawa Pharmaceutical Co. from a strain of Streptomyces was found to also possess potent antitumor activities against a broad range of cancer cells, promoting microtubule assembly in vitro and inducing G2/M phase arrest in the cell cycle [30]. Methot and Roush reported a solvent dependent vinylogous MBH reaction route to the synthesis of the tricyclic core (80) of FR182877 (82) (Scheme 11) [31]. They showed that although using tert-amylalcohol as medium gave a
diastereomeric mixture of the desired product (80) and a regioisomeric product (81), in the presence of THF:H$_2$O (3:1) 80 was formed as the sole product.

2.1.9. Syributins

Krishna and co-workers accomplished the total synthesis of syributins 1 (88) and 2 (89) from a diastereomeric mixture of the MBH adduct (84) of 2,3-O-isopropylidene-R-glyceraldehyde and ethyl acrylate (Scheme 12) [32]. Interestingly they found that performing the MBH reaction in dioxane-water not only afforded the product at normal temperature and pressure but also enhanced the stereoselectivity in favour of S-isomer. The reduction of the ester group in 84 gave the primary alcohol 85 that upon reaction with acryloyl chloride furnished a diene 86. Ring closing metathesis in the presence of Grubbs 1$^{st}$ generation catalyst gave an advanced intermediate 87. This was then transformed into the syributins 1 and 2.

2.1.10. (+)-Tubelactomicin A

Tubelactomicin A (94), a 16-member macrolide antibiotic, was first isolated from the culture broth of Nocardia sp. MK703-102F1 [33]. Tadano and co-workers achieved the total synthesis of natural (+)-tubelactomicin A in 54 steps from methyl (R)-lactate (90) in 6.2% overall yield using the MBH reaction between 91 and methyl acrylate as one of the key steps (Scheme 13) [34].

2.1.11. Dihydroeponemycin

Dihydroeponemycin (100), an active derivative of eponemycin targets the subunits of both constitutive proteasome and immunoproteasome. Kim et al. developed an improved route to the synthesis of hydroxymethyl substituted enone 97 and transformed it to the natural dihydroeponemycin via combination of Wittig–Horner and Baylis–Hillman type two-step “one-pot” reaction [35]. Initial reaction of Boc–Leu–OMe (95) with dimethyl methylphosphonate gave the precursor 96 which served as the substrate for the one-pot reaction to afford 97 in good yields. Subsequent protection and epoxidation gave the epoxy derivative 98 which upon amide coupling yielded the dihydroeponemycin 100 (Scheme 14).

2.1.12. (S)-4,5-dihydroxy-2,3-pentanedione (DPD)

Autoinducers are extremely important for many bacterial species to increase their population. Among various autoinducers, identified so far, a borate, known as autoinducer-2 (AI-2), formed from the metabolic product (S)-4,5-dihydroxy-2,3-pentanedione (DPD) is produced by a large number of both Gram-negative and Gram-positive bacteria [36]. Doutheau et al. developed a DABCO-catalyzed MBH reaction between 2-(tert-butyldimethylsilyloxy) ethanol (101) and 3-buten-2-one in THF to obtain the adduct 102 which after reductive ozonolysis of the double bond resulted into racemic DPD. They also applied the same sequence to other sub-
strates for preparing the chain elongated analogues of DPD (Scheme 15) [37]. They found that along with the acyclic form the two cyclic anomers remain in equilibrium.

In an extension of their work, subsequently they reported an asymmetric synthesis of trifluoromethyl analogue of DPD [38]. The CF$_3$-group was introduced by reacting TMSCF$_3$ with the $\alpha$-methylene ester 109, which was prepared from the MBH reaction between (tert-butyldimethylsilyloxy) acetaldehyde (101) and HFIPA (Scheme 16).

2.1.13. Luminacin D

Jogireddy and Maier disclosed a novel route to the synthesis of Luminacin D (123), an angiogenesis inhibitor isolated from the soil bacteria Streptomyces sp. Mer-VD1207 [39]. Several Luminacin derivatives showed antitumor activity with IC$_{50}$ values of less than 0.1 mg/mL in a rat aorta matrix culture model [40]. The starting material for the synthesis was prepared by a simple MBH reaction between propanaldehyde (120) and methyl acrylate. Then by OH transposition and two highly stereoselective asymmetric aldol reac-
vanadium-mediated epoxidation afforded the epoxide DMP oxidation, HWE reaction, desilylation and epoxidation. A seven step sequence involving silylation, DIBAL-H reduction, the methyl ester 125 which was transformed to the epoxide 128 stereoselectively (Scheme 18). This epoxide was the common precursor to the two natural products.

2.1.14. (+)-Fostriecin and (+)-Phoslactomycin B

Phoslactomyons A–F and I produced by the soil bacteria species Streptomyces belongs to the phoslactomycin family of antifungal and antitumor antibiotics together with fostriecin [41]. In addition, these compounds are selective inhibitors of serine/threonine phosphatase 2A and presumed to be responsible for their antitumor activity. Hatakeyama et al. reported the formal asymmetric synthesis of (+)-fostriecin and (+)-phoslactomycin B from a common intermediate 128 resulting into a general route to phoslactomycin family [42]. Initially a β-ICD-catalyzed MBH reaction between 3-(4-methoxybenzyloxy)propanal (124) and HFIPA gave the adduct 125 in 58% yield and 99% ee. Thereafter, methanolation of 125 gave the methyl ester 126 which was transformed to the epoxide 128 via a seven step sequence involving silylation, DIBAL-H reduction, DMP oxidation, HWE reaction, desilylation and epoxidation. A vanadium-mediated epoxidation afforded the epoxide 128 stereoselectively (Scheme 17). This epoxide was the common precursor to the two natural products.

2.1.15. Gabosine

Gabosines, the naturally occurring cyclitol, were isolated from Streptomyces strains and were found to display biological activities like antibiotic, anticancer, and DNA binding properties [43]. Shaw and co-workers used DMAP-catalyzed MBH reaction as one of the key steps to accomplish the syntheses of (-)-gabosine E (139) and (+)-4-epi-gabosine E (140) starting from methyl α-D-glucopyranoside and methyl α-D-mannopyranoside, respectively (Scheme 19) [44]. They demonstrated that the presence of an acetyl group at C-6 position of sugar-derived cyclic enone (137) prevented the aromatization of the MBH adduct 138 formed via the reaction between the enone and formaldehyde.

Later in an alternate approach, Krishna and Kadiyala reported a combination of diastereoselective MBH reaction and RCM reaction as a flexible route to readily access the cyclohexenoid skeletons.
The cyclohexenoids were synthetically manipulated further to obtain gabosine I, gabosine G and epi-gabosine I (Scheme 20) [45].

Very recently Chanti Babu et al. reported the synthesis of gabosine C and other related analogues by applying RCM reaction followed by MBH reaction strategy (Scheme 21) [46].

2.2. Natural Products of Fungus Origin

2.2.1. Mycestericine E

(-)-Mycestericin E (167) is a potent immunosuppressive agent, isolated from the culture broth of the fungus Mycelia sterilia ATCC 20349 [47]. Hatakeyama and co-workers reported an enantio- and diastereo-controlled synthesis of this natural compound [48]. The key step of the sequence was a β-ICD-catalyzed asymmetric MBH reaction between aldehyde 161 and HFIPA to obtain the enantiomerically pure adduct 162 in 47% yield. Transforming 162 to its methyl ester followed by Sharpless epoxidation gave the epoxy derivative 163, which was converted to the epoxytrichloroacetimide 164 that upon BF₃·OEt₂-mediated cyclization resulted into the formation of an oxazolidine 165 stereoselectively (Scheme 22). A sequential Moffatt oxidation, NaClO₂ oxidation and esterification of 165 furnished the methyl ester 166 which after de-protection and saponification afforded (-)-mycestericin in 4.7 % overall yield.
2.2.2. Mniopetals

Mniopetals A-F are drimen type sesquiterpenes isolated from Mniopetalum sp. 87256 and demonstrated to be inhibitors of HIV reverse transcriptase [49]. Jauch in 2001 reported the total synthesis of mniopetal F (173) from the MBH adduct prepared via lithium phenyl selenide promoted reaction between an aldehyde 169 and Feringa’s butenolide 170. Subsequently an endo-selective intramolecular Diels-Alder reaction (IMDA) gave 172 which upon inversion of the hindered secondary alcohol and a new variant of Perkin-Doering oxidation gave the title compound. The total synthesis was 14 steps long with an overall yield of 10% (Scheme 23) [50].

By employing the same methodology, the total synthesis of mniopetal E (174) was achieved (Scheme 24) [50b].

In another approach, a solid phase MBH reaction was applied to the resin bound aldehyde 175 to accomplish the synthesis of the tricyclic core (177) of the mniopetals which is delineated in Scheme 25 [50c].

2.2.3. (+)-Harziphilone

Harziphilone (182) is a novel fungal metabolite isolated from the extract of the fermentation broth of Trichoderma harzianum [51]. It has the inhibitory activity against the binding of REV protein to PRE-RNA with IC50 values of 2.0 μM. Besides it shows cytotoxicity at 38 μM against the murine cell line M-109. Sorensen and co-workers applied a vinylogous MBH reaction for the successful synthesis of (+)-harziphilone (Scheme 26) [52]. An intramolecular 1,4-addition reaction results into an allenoate ion 179 which upon proton transfer transforms into zwitterion 180. Thereafter the nucleophilic catalyst is eliminated via a β-elimination to yield 181 which undergo a 6π-electrocyclization to furnish (+)-harziphilone (182).

2.2.4. Phaseolinic Acid

Paraconic acids, a group of highly substituted γ-butyrolactones isolated from moss, lichens, fungi and cultures of Penicillium sp. were reported to display a broad spectrum of biological activities like antitumor, antifungal and antibacterial [53]. Selvakumar and

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Scheme 22.

Scheme 23.

Scheme 24.

Scheme 25.
co-workers developed an approach for the synthesis of butenolides, the core unit of the class of natural products [54]. The protocol involved an initial MBH reaction to obtain the adduct 184 which was acryloylated to 185, followed by RCM reaction between two electron deficient dienes to produce 186. It was then employed for the synthesis of (±)-phaseolinic acid 188 (Scheme 27).

2.2.5. Methyl-7-dihydro-trioxacarcinoside B

Koert et al. achieved the synthesis of methyl-7-dihydrotrioxacarcinoside B (192), a branched octose from the quinocyclines utilizing the MBH adduct 189 [55]. The enzymatic resolution of the MBH adduct with Pseudomonas AK20 (Amano) afforded the product in >99% ee. A highly anti-selective reduction of the ketone and a RCM reaction were the key steps employed for transforming MBH adduct to the cyclic intermediate 191. Further substrate-controlled stereo-selective epoxidation and a regio- and stereo-selective epoxide ring opening by allyl alcohol were used to introduce the C(3)-OH group as required in methyl-7-dihydrotrioxacarcinoside B 192 (Scheme 28).

2.2.6. Sphingofungins

Sphingofungins E and F, two highly oxygenated α-quaternary amino acids were isolated from the fermentation broth of Paecilomyces variotii in 1992 [56]. Wang and Lin developed a flexible
approach for the asymmetric syntheses of sphingofungins E (199) and F (202), with efficient use of the MBH adduct [57]. The synthesis was initiated with the MBH reaction of L-(+)-tartaric acid derived aldehyde 193 with methyl acrylate under neat condition. Sharpless dihydroxylation followed by mesylation and base mediated epoxidation gave the epoxy derivative which was then reduced to afford 196, a common substrate for the synthesis of both the natural compounds (Schemes 29 and 30).

### 2.2.7. Oidiodendrolides

Tetranorditerpene dilactones oidiolactones A-D (210-213) are produced by the filamentous fungi represented by Oidiodendron truncatum and Oidiodendron griseum whereas the podolactones such as nagilactone F (214) are produced by different species of the Podocarpus plant [58, 59]. The podolactones are associated with very good biological activities like antifungal, antitumoral, antifeedant, etc. Hanessian and co-workers developed an efficient and high-yielding strategy for the synthesis of these biologically active dilactones by using MBH reaction, the stereocontrolled construction of /γ/-lactone via bromolactonization, and catalytic Reformatsky type reaction as the key steps [60]. By employing these reactions, a common intermediate 207 was prepared which was then successfully converted to CJ-14,445, LL-Z1271γ, oidiolactones A, B, C, and D, and nagilactone F in good yields via several steps (Scheme 31).

### 2.2.8. Cyclitol

MK7607 (221), an unsaturated carbapyranose, was isolated from Curvularia eragrostidis D2452 [61]. Another compound (+)-streptol (222), a C-4 epimer of MK7607, isolated from the cul-
ture filtrate of an unidentified Streptomyces sp., inhibited the germination of lettuce seedlings [62]. Krishna and Kadiyala reported the synthesis of these cyclitol analogues from (R,R)-tartaric acid by using MBH and RCM reactions as the two key steps to construct the diastereomeric cyclohexenoids which were independently transformed into the target compounds (Scheme 32) [63]. The substrate 216 was prepared from (R,R)-tartaric acid by following the literature method [64].

2.2.9. Trichodermine A

Trichodermine A (229) was isolated from the strain Trichoderma sp. YLF-3 and was reported to possess potent antibacterial properties [65]. Krishna and Kadiyala applied their MBH/RCM strategy for obtaining this natural compound too [66]. The synthesis was initiated by performing MBH reaction between acetaldehyde and ethyl acrylate to obtain the adduct 224. A Sharpless kinetic resolution of 224 gave the MBH adduct as (S)-isomer. After a series of reaction, the homologation of this adduct was accomplished to obtain the bis-olefin 227. RCM reaction in Hoveyda-Grubbs II catalyst (10 mol%) successfully afforded the MOM protected cyclopentenol 228 which was de-protected to obtain 229 in good yields (Scheme 33).

2.2.10. Isoaspinonene

Krishna and co-workers extended the application of MBH reaction for the total synthesis of isoaspinonene (235), a secondary metabolite isolated from the cultures of Aspergillus ochraceus [67]. In this case the synthesis was initiated from a chiral aldehyde 230 that could be readily generated from racemic propyleneoxide. The MBH adduct of this aldehyde and ethyl acrylate was isolated in excellent yield (85%). This MBH adduct was first transformed to a cyclic ether 232 from 231 in five steps. A sequential chelation-controlled
2.2.11. (+)-Lysergic Acid

(+)-Lysergic acid (241), a member of pharmacologically important Ergot alkaloids, was isolated from the fungus Claviceps purpurea. Very recently, Jia and co-workers reported two different enantioselective strategies featuring metal-catalyzed reactions to achieve the total synthesis of (+)-lysergic acid [68]. In one of their approaches they used the allyl bromide 238, prepared from the MBH adduct of formaldehyde, to generate the precursor 239 for RCM reaction (Scheme 35).

3. NATURAL PRODUCTS OF MOSS ORIGIN

3.1. (+)-Ricciocarpine A

(+)-Ricciocarpine A (244), the furanosesquiterpene which was isolated from the liverwort Ricciocarpus natans exhibits very good molluscidal activity against the water snail Biomphalaria glabrata [69]. Krische and Agapiou reported a vinylogous MBH reaction [70]. They found that the enone-enoate was not reactive in the PBu reaction with 239; prepared from the MBH adduct of formaldehyde, to generate the precursor 239 for RCM reaction (Scheme 36).

3.2. Palhinine Core

Isopalhinine A (256), a lycopodium alkaloid was isolated from the nodding club moss Palhinhaea cernua [71]. It is characterized with a complex pentacyclic framework. Very recently Sizemore and Rychnovsky reported a MBH/IMDA strategy to construct the isotwistane core of palhinine natural products [72]. The MBH/IMDA reaction sets the vicinal all carbon stereocenters of the natural product's core 251 of delphinium alkaloid cardionine 257. But the IMDA reaction of 248 using TMSCI/Et3N and heating at 90 °C in DMF afforded the isotwistane core 255 of isopalhinine (Scheme 37).

4. NATURAL PRODUCTS OF TERRESTRIAL ORIGIN

4.1. Alkaloids

4.1.1. Quinine

Webber and Krische accomplished the stereoselective formal synthesis of (±)-quinine in 16 steps and 4 % overall yield from aminoacetaldehyde dimethylacetal [73]. The hallmark of the synthesis was a catalytic enone cycloallylation that combines the nucleophilic feature of MBH reaction and electrophilic feature of Tsuji-Trost reaction. Using these reactions they transformed the intermediate 258 to the tetrahydropyridine 259 in 68% yields. Reducing 259 in the presence Cul/DIBAL-H gave the piperidine 260 which was transformed to (+)-7-hydroxyquinine in highly stereoselective manner. Indeed they could obtain the (+)-7-hydroxyquinine in 13 steps and 11% overall yield (Scheme 38). However their attempt to deoxygenate the C-7 hydroxyl group was unsuccessful. This led them to perform C-7 deoxygenation before the amine epoxide cyclization. Hence the piperidine 259 was initially transformed to enone 263 which after reduction to alcohol, acetylation and formate-mediated reduction gave the advanced intermediate 265 which was reported [74] to afford quinine in 4 steps (Scheme 39).

4.1.2. Grandisines

Grandisine alkaloids which were isolated from the leaves of the Australian rainforest tree Elaeocarpus grandis exhibit affinity for the human δ-opioid receptor [75]. Tamura and co-workers completed the synthesis of grandisine D (269) by using an aldol reaction of 8-formylindolizidine 268 with (S)-5-methycyclohexenone [76]. The key intermediate 8-formylindolizidine (268) was synthesized using a Brunsted acid mediated stereoselective MBH ring-closure reaction of 267 via acyl iminium ion (Scheme 40).
Scheme 37.

Scheme 38.
Scheme 39.

Scheme 40.

Scheme 41.

The same group extended this protocol to the synthesis of grandisine B (272), 9-epi-ent-grandisine B (275) and 9-epi-ent-grandisine D (274). Grandisine B was synthesized by using grandisine D as the biogenetic precursor (Scheme 41) [77]. The isoquinuclidinone of grandisine B was formed from grandisine D by an intramolecular imine formation.

4.1.3. (+)-Heliotridine and (-)-Retronecine

Aggarwal et al. reported a novel methodology in which a broad range of Michael acceptors were allowed to couple with the readily available iminium ion in inter- and intramolecular MBH type reaction to afford densely functionalized heterocycles [78]. The iminium ions, generally present as masked N,O-acetals, were generated...
by TMSOTf, while BF₃·Et₂O in the presence of Me₂S was used to achieve the target. More importantly, the process was highly enantioselective for cyclic enones. As an application of the protocol, they formulated a short synthesis of (+)-heliotridine (279) and (-)-retronecine (280), as shown in Scheme 42.

4.1.4. (-)-Trachelanthamidine

Synthesis of pyrrolizidine nucleus was also demonstrated by Kamimura via an aza-Baylis-Hillman equivalent reaction followed by RCM reaction [79]. They showed that the optically active MBH adduct 283 underwent a two-step conversion to N-allyl-β-amino-R-methylene ester 285 in high yield, which gave chiral 2,5-dihydropyrrole 286 through RCM reaction catalyzed by Grubbs II catalyst. The 2,5-dihydropyrrole was further transformed to the pyrrolozidine (287) framework which was the precursor for the total synthesis of (-)-trachelanthamidine (Scheme 43) [80].

4.1.5. Vibsanin E

Vibsanin E (294) was first isolated from Viburnum awabuki by Kawazu [81]. Later Fukuyama et al. determined the absolute stereochemistry of this natural compound [82]. Williams et al. reported a protecting group-free approach for constructing the a protecting group-free approach for constructing the tricyclic core of vibsanin E [83]. The tricyclic system was prepared via an acid-catalyzed reaction of 291 which was obtained via the Gaiéd-modified Baylis-Hillman reaction of the cyclic enone 290. Subsequently by a retro-Claisen/Claisen reaction, the CO₂Et group was incorporated and by Zercher reaction the ring was expanded to achieve the synthesis of tricyclic core 293 of vibsanin E (Scheme 44).

4.1.6. Tacamonine

Tacamonine (300) is one of the few tacamane type indole alkaloids and was first isolated in 1984 from Tabernaemontana eglandulosa [84]. Tacamonine is known for its vasodilator and hypotensive activities. Chang et al. developed a one-pot synthesis of N-alkyl 3-(E)-alkylidene-5-substituted sulfonylpiperidine-2,6-diones via a [3+3] annulation between N-alkyl α-subsituted sulfonyl acetamides and α,β-unsaturated esters obtained via the MBH reaction [85]. In their attempt to highlight the application of the protocol for the synthesis of natural product, they demonstrated that the sulphonyl acetamide 296, derived from tryptamine, undergoes similar transformation to afford piperidine-2,6-dione 297 that was
transformed to an advance intermediate 299 for the synthesis of tacamonine (Scheme 45) [86].

4.1.7. Strychnos Alkaloids

Andrade and Sirasani developed a sequential one-pot bicyclization route to the synthesis of tetracyclic framework of Strychnos alkaloids [87]. Their protocol involved a AgOTf-mediated spirocyclization of appropriately functionalized indole 3-carbinamide 301 to afford the intermediate 302 which in the presence of DBU underwent an intramolecular aza-MBH reaction to afford the tetracyclic core 303 of Strychnos alkaloid (Scheme 46).

Later they extended the cascade protocol involving spirocyclization/aza-Baylis-Hillman reaction for the synthesis of (-)-akuamicine 308 and (+)-strychnine 310 from appropriately substituted intermediate 307 and 309, respectively (Schemes 47 and 48) [87b].

Extending the scope of their protocol, this group also developed the total synthesis of another indole alkaloid (-)-leuconicine A and B (Scheme 49) [87c].

4.1.8. Neocryptolepine

Neocryptolepine, an indoloquinoline alkaloid isolated from Cryptolepis sanguinolenta exhibit potent antimalarial activity against chloroquine-resistant strains of P. falciparum. Basavaiah and Reddy developed a one-pot strategy for the synthesis of α-carbolines from MBH acetates [88]. Their synthesis involved
three key reaction steps: mono alkylation of 2-nitroarylacetonitriles with MBH acetates [89], chemoselective reduction of nitro group into amino group using Fe/AcOH and formation of two rings. They employed this strategy to the synthesis of indoloquinoline alkaloid neocryptolepine (318) in 22% overall yield (Scheme 50).

4.1.9. Grandiamide

Grandiamide D (324), gigantamide A (328) and dasyclamide (327) were isolated by Duong et al. from the leaves of Aglaia gigantean [90]. Very recently Ilangovan and Saravanakumar reported the synthesis of these natural products by using MBH adduct 320 as the common intermediate [91]. They showed that the MBH reaction of ethyl acrylate with aldehyde 318 afforded the racemic adduct 320 which was then converted to the intermediate 323 and dasyclamide 327 via EDCI coupling reaction. Dasyclamide was then converted to gigantamide A by PCC oxidation method (Scheme 51).

4.2. Terpenoids

4.2.1. Mikanecic Acid

Mikanecic acid (332), a terpenoid dicarboxylic acid was isolated from the products of alkaline hydrolysis of the alkaloid mikanoidine obtained from Senecio mikanioides otto [92]. Basavaiah et al. reported a simple two-step route involving sequential Diels-Alder reaction and saponification to prepare this terpenoid. Initially the MBH adduct 329 was converted in situ to the diene 330 which underwent a stereoselective Diels-Alder reaction to produce 331 which upon hydrolysis in the presence of KOH gave mikanecic acid in good yield (Scheme 52) [93].

4.2.2. (+)-Arnicenone

(+)-Arnicenone (342), an isocomene-type angular triquinane sesquiterpene isolated from the essential oil of rhizomes and roots of Arnica plants, was synthesized by Ogasawara and co-workers by using MBH adduct 9 as the starting material [94]. A Dibal-H reduction of 9 gave 10 which upon NBS-mediated regioselective olefin protection furnished 333 in excellent yields. The Eschenmoser rearrangement reaction with 333 was used for the diastereoselective formation of the exo-acetamide 334 which was transformed to the propargyl derivative 335. The Pauson-Khand reaction with 335 afforded the polycyclic enone 336 as an epimeric mixture. The tricyclic core 337 was prepared in 10 steps from 336 using retro-Diels-Alder reaction and Wolf-Kishner reduction as one of the key steps. The tricyclic compound 337 was subsequently converted to (+)-arnicenone by methylation and exo-methylketone formation (Scheme 53).
4.2.3. Clerodane Decalin Core

The clerodane class of natural products is diterpenes that exhibit potent antiproliferative activity against several types of human-cancer-cell lines. Schaus et al. formulated an asymmetric synthetic protocol toward the synthesis of clerodane decalin core of asmarine via a two-step ring-annulation procedure \[95\]. The first step of the synthesis to construct the core of clerodane was the asymmetric MBH reaction of cyclohexenone \[245\] with aldehydes \[343\] promoted by Et$_3$P and binaphthol-derived Brønsted acids whereas the second step involved BF$_3$.OEt$_2$-catalyzed intramolecular Hosomi–Sakurai reaction as outlined in Scheme 54.

4.2.4. ABC Core of Neovibsanins

Neovibsanins A and B, members of vibsane class of diterpenoids exhibit unique activity of promoting neurite outgrowth of NGF-mediated PC-12 cells. Mehta and Bhat demonstrated the utility of MBH adduct to achieve the synthesis of the tricyclic core furo-furanone \[351\] of neovibsanin alkaloids \[96\]. An initial MBH reaction of suitably decorated cyclohexenone \[290\] with formaldehyde gave the adduct \[291\] (Scheme 55). Protecting the hydroxyl group gave \[349\] which upon addition of propargyl alcohol afforded \[350\]. A series of reactions with \[350\] resulted into the tricyclic core of neovibsanins in good yields.

4.2.5. ABC and FGH Segments of Rubrifloradilactone C

Rubrifloradilactone (361), isolated from Chinese medicinal plants is a Schisandra nortriterpenoid bearing an eight-ring framework and is ascribed with potent anti-HIV and cytotoxic activity \[97\]. Mehta and co-workers also reported the synthesis of ABC and FGH segments of rubrifloradilactone C using the MBH adduct \[355\] prepared from cycloheptenone. Similar to the synthesis of neovibsanin core \[351\], here too adding propargyl alcohol to the OH-protected MBH adduct \[356\] resulted into \[357\] which was then converted to the allyl alcohol \[358\] (Scheme 56). It was disclosed that oxidation of the primary alcohol \[359\] to aldehyde via MnO$_2$ resulted into the tricyclic ABC core \[360\] via oxa-Michael reaction followed by lactonization cascade.
Scheme 53.

Scheme 54.
Scheme 55.

Scheme 56.

Scheme 57.

The FGH core 367 of rubrifloradilactone C was achieved by almost similar route using OH-protected MBH adduct 363 and using the propargylic alcohol 366 instead of allyl alcohol in oxidation followed by lactonization reaction (Scheme 57) [98].
4.3. Lignans

4.3.1. Eupomatilones

Eupomatilones (374, 375) are structurally novel lignans which were isolated in 1991 by Carrol and Taylor from the shrub *Eupomatia bennettii* [99]. They are characterized by a biaryl system with a substituted γ-lactone ring system attached to one of the aryl rings. Kabalka and Venkataiah reported the synthesis of these natural products by constructing the γ-lactone from the homoallylic alcohols which in turn were prepared from the intermediates afforded from the MBH adduct [100]. Whereas, treating the boronate 368 with the biphenyl aldehyde in the presence of Lewis acid afforded the alcohol 372 and 373 in low yields, the Barbier allylation of identical substrate with allyl bromide 369 furnished the same alcohols in good yields (Scheme 58). Intramolecular cyclization of the alcohol under mild acidic condition using PTSA gave the lactone leading to completion of synthesis of eupomatilone 2 (374) and 5 (375). Further, isomerisation and reduction of the double bond of the lactone provided access to *epi*-eupomatilone 6 (376).
4.3.2. (±)-Yatein, (±)-Podorhizol and (±)-epi-Podorhizol

Coelho and co-workers demonstrated a simple and efficient method for the diastereoselective preparation of hydroxylated β-piperonyl-γ-butyrolactones and extended this protocol to the synthesis of the biologically active lignans (±)-yatein (382), (+)-podorhizol (380) and (±)-epi-podorhizol (381) (Scheme 59) [101]. These lignans are endowed with interesting biological properties such as insect feeding deterrent and anti-viral activity (yatein), moderate anti-tumor activity (podorhizol) and antibacterial activity (epi-podorhizol). The butyrolactones were prepared by direct oxidation of lactol, which was synthesized in one step from the cyanideester 380 using reductive conditions. They prepared the cyanide ester 378 by a diastereoselective Michael addition reaction of β-deoxy-b-glucose with the MBH adduct as Michael acceptor afforded the syn-isomer while β-ketoester of the corresponding adduct afforded the anti-isomer stereoselectively.

4.4. Others

4.4.1. Methyl Jasmonate

Methyl jasmonate (385) was first isolated from Jasminum grandiflorum and later from Rosmarinus officinalis. It is of paramount importance to the fragrance industry because of its elegant and radiant jasmine scent. This molecule was commercialized by Firmenich SA under the trade name of Hedione®. Chapuis and co-workers accomplished the synthesis of the jasmoid skeleton with versatile stereocontrol and modification to the C(2) side chain (Scheme 60) [102]. The three key steps of the process were MBH reaction of a suitable aldehyde with cyclopentene-1-one in the presence of Bu₃P to obtain the adduct 383 followed by MeC(O)(Me)₃, PivOH-mediated orthoester Claisen rearrangement affording 384. A Pd/Al₂O₃-mediated reduction of the double bond in 384 gave the corresponding analogues of methyl jasmonate 385. However in terms of fragrance none of the synthetic analogues was found to be better than the natural compound.

4.4.2. Umbelactone

Umbelactone-1 is one of the examples of naturally occurring γ-(hydroxymethyl)-α,β-butenolide isolated from Memecylon umbellatum Brum and the crude extracts of this plant elicit a broad spectrum of bio-activities including antiviral (against Ranikhet disease virus), antiinflammatory and spasmodytic [103]. Kamal et al. developed a lipase-mediated chemoenzymetic resolution protocol to prepare both isomers of umbelactone-1 [104]. The synthesis was initiated with the MBH reaction of aldehyde 387 with methyl acrylate in MeOH as medium to obtain the adduct 388 which was transformed to the allylic alcohol 389 by following a series of known reactions (Scheme 61). Resolution of this allylic alcohol with lipase PS-C (Pseudomonas cepacia immobilized on modified ceramic particles) in vinyl acetate gave the (R)-isomer 390 as acetate and as (S)-isomer 391 as alcohol. A sequential acryloylation, RCM reaction and debenzylation furnished 390 and 391, the respective enantiomers of umbelactone-1.
positive and Gram-negative strains of bacteria and certain fungi tolerant strains of bacteria. Ubukata and co-workers disclosed the synthesis of (+)-6-tuliposide B from D-glucose in nine steps using MBH reaction as the key step [105]. The MBH reaction of 2-(tert-butyldimethylsilyloxy)-acetaldehyde (101) with 6-O-acryloyl-1-O-(2-trimethylsilylethyl)-D-glucopyranoside (397) followed by a mild de-protection procedure using TFA in CH₂Cl₂ gave the natural compound 399 (Scheme 62). The interesting feature of their protocol was that both isomers of the MBH adduct were used to synthesize the (+) and (-) isomers of tuliposide-B. In order to confirm the structure of the prepared compound, these workers transformed each of them to (-)-tulipalin B (400) and (+)-tulipalin-B (402).

Subsequently this group developed an alternate protocol for the synthesis of (+)-tuliposide B where the sugar part was introduced at the later stage of the reaction sequence [106]. A stereoselective MBH reaction of 318 with N-acryloyl camphor sultam 403 was the key step in this approach (Scheme 63).

**4.4.4. Onychine**

Onychine (414), a 4-azafluorenone natural product was isolated from the trunkwood of the Brazilian tree *Onychopetalum amazoni-
It shows potential antimitotic activity against *C. albicans*. Clary and Back initiated the total synthesis of onychine by preparing tetrahydropyridine intermediate (411) via a vinylogous azomethine MBH reaction of 1-((benzylidene)benzenesulfonylamide) with methyl 2,4-pentadienoate (410) [108]. A sequential saponification, acid chloride formation and intramolecular Friedel-Craft’s reaction on 411 resulted into the 4-azafluorenone core 412.

### 4.4.5. (±)-Leiocarpin A

Leiocarpin A (423) and Goniiodiol (422) are two pyranopyrone containing natural compounds, isolated from the *Goniobothalamus* Sp. and have been reported to display anticancer activity. Paioti and Coelho disclosed a diastereoselective approach for the total synthesis of (±)-leiocarpin A and (±)-goniodiol starting from the MBH adduct of benzaldehyde [109]. These biologically active steryl lactones were synthesized from a common α,β-unsaturated lactone intermediate 421, prepared in five steps and 40% overall yield, from the MBH adduct 416. They found that under basic condition the lactone 421 directly afford leiocarpin A (423), while under acidic condition it gave (±)-goniodiol (422) (Scheme 65).

### 4.4.6. Isoparvifuran

Isoparvifuran (429) is an antifungal agent isolated from the heartwood of *Dalbergia parviflora* [109]. Namboothiri et al. accomplished the first total synthesis of isoparvifuran by using MBH reaction as the key step [110]. An initial MBH reaction between nitrostyrene 424 and ethyl-2-oxoacetate afforded 425, which upon base-mediated addition of phenol gave the benzofuran 426 in 76% yield (Scheme 66). Alkaline hydrolysis of the ester group in 426 followed by CuO-NaOH-mediated decarboxylation gave benzylated Isoparvifuran 428 in 80% yield. De-protection of the benzyl group by Pd-catalyzed hydrogenolysis afforded the natural product isoparvifuran 429 in an overall yield of 47% for six steps.

### 5. NATURAL PRODUCTS OF MARINE ORIGIN

#### 5.1. Epoxycydon

Epoxycydon (439) and *epi*-epoxycydon (438) are two epoxycyclohexenone-based natural products isolated from the *Aspiospora monagnei* Saccardo, a fungal endophyte isolated from the inner
tissue of the North Sea algae Polysiphonia violacea. They possess interesting antifungal, antibacterial and phytotoxic activity. Taylor and Genski unveiled an Et<sub>3</sub>N/nBu<sub>3</sub>P-catalyzed MBH reaction between an O-protected epoxidised hydroxyquinol (436) and paraformaldehyde to synthesize (±)-epi-epoxydon (438) (Scheme 67) [111]. The synthesis started with the Diels-Alder reaction between p-benzoquinone (431) and cyclopentadiene (430) to obtain 432 which was then transformed to the epoxyquinol derivative 435.

5.2. N-Boc-dolaproine

Almeida and Coelho reported a stereoselective total synthesis of N-Boc-dolaproine (Dap), an amino acid residue of the antineoplastic pentapeptide dolastatin 10 (445). The initial step of the synthesis involved MBH reaction between N-Boc-prolinal (440) and methyl acrylate under ultrasound condition to furnish the adduct 441 (Scheme 68) [112]. A diastereoselective double bond hydrogenation in 441 yielded the intermediate 442 which upon hydrolysis of the ester group gave O-methyl-N-Boc-dolaproine 443. Simultaneously, methyl group de-protection of the ester group in 442 afforded 444.

5.3. Salinosporamide

Salinosporamide A (450) is a bioactive natural product of a marine organism that is widely distributed in ocean sediments. It is an effective proteosome inhibitor with in vitro cytotoxic activity.
against several tumor cell lines with IC$_{50}$ values in nanomolar range. Corey et al. utilized an intramolecular MBH reaction between keto group and acrylamide subunit for the cyclization to produce a highly substituted 4-methylene-5-oxo-pyrrolidine derivative (449), which served as the starting material in the enantioselective total synthesis of salinosporamide A (Scheme 69) [113].

5.4. Halichlorine Spiro Subunit

Clive et al. reported the synthesis of bicyclic amines with nitrogen at a ring-fusion position via a sequential MBH reaction between N-protected β-amino aldehydes 451 and acrylates followed by O-acetylation and N-deprotection, as shown in scheme 70. They extended this strategy to the synthesis of the halichlorine’s spiro subunit 455 [114].

5.5. (+)-Hippospongic Acid A

(+)-Hippospongic acid A (463) which was isolated from the marine sponge *Hippospongia sp.* bears a triterpenoid structure and is known to inhibit gastulation in starfish embryos. In addition to this it is also found to exhibit modest inhibitor of both DNA polymerase (IC$_{50} = 5.9-17.5$ nM), and DNA topoisomerase I/II (IC$_{50} = 15-20$ pM), the two enzymes responsible for DNA replication [115]. Further, this molecule is effective at inducing apoptosis in the human gastric cancer cell line NUGC-3 by arresting the cell cycle at G1/G2. Trost et al. utilized a Pd-catalyzed DYKAT of MBH adducts 458 to achieve the total synthesis of (+)-hippospongic acid [116]. The DYKAT cyclization substrate was obtained via two MBH reactions and one Claisen rearrangement. Subsequently by DYKAT cyclization strategy they could synthesize the pyran ring with required stereocenter which after a series of reactions afforded (+)-hippospongic acid in enantiomerically pure form (Scheme 71).

5.6. C1–C11 Fragment of Caribenolide I

Franck et al. successfully synthesized the C1-C11 fragment (467) of caribenolide I (468), a 26-membered macrolactone that possesses in vitro cytotoxicity against human colon tumor cells (T/C = 150% at a dose of 0.03 mg/kg), starting from the MBH reaction between 3-para-methoxybenzyloxypropanal (124) and methyacrylate in the presence of 3-HQD, as illustrated in Scheme 72 [117]. The stereogenic centres at C2, C3 and C10 were controlled during the aldol reaction of the aldehyde 464 using thioxazolidinone moiety as the chiral auxiliary.

5.7. Semiplenamide C and E

Semiplenamide, the naturally occurring fatty acid derivatives, isolated from the marine cyanobacterium *Lyngia semiplena* possess potent toxicity towards the brine shrimp model system [118].
allyl bromide 470 obtained from the MBH adduct 469 was used for the synthesis of this natural compound by Das et al. [119]. The EDCI coupling between 472 and (S)-alaninol afforded the allyl amide 473 which was converted to the semiplenamide C and E by simply acetyling the hydroxyl group (Scheme 73).

5.8. (±)-Spisulosine (ES285)

Coelho et al. developed a novel approach to diastereoselective total synthesis of the anti-tumoral agent (±)-spisulosine (481) which was isolated from the extracts of Spisulapolynyma [120]. The synthesis of the target natural compound involved the initial formation of an acyloin 479 from the MBH adduct of the aldehyde 476 which was subsequently used in a highly diastereoselective reductiveamination reaction to produce 480. The deprotection of 480 afforded (±)-spisulosine in 10% overall yield (Scheme 74).

5.9. Sporolide Precursor

Gademann and co-workers utilized the MBH adduct (363) prepared from cyclopentene-1-one (362) and formaldehyde for the synthesis of a precursor 485 of marine macrolide sporolides, iso-
lated from the marine bacterium *Salinispora tropica* (Scheme 75) [121].

### 5.10. Pericosine

Pericosines, a class of densely oxygenated cyclohexenoid natural products, were isolated from the sea hare *Aplysia kurodai* and are found to be cytotoxic metabolites of the fungus *Periconia byssoidea* OUPS-N133 [122]. Besides they have significant activity against the murine P 388 cell lines and human cancer cell lines [123]. Vankar and co-workers reported MBH reaction followed by RCM reaction mediated route for the total synthesis of pericosine B and pericosine C and their enantiomers from D-ribose (Scheme 76) [124]. Their synthesis started with substrate 489 derived from commercially available D-ribose 488 [125].

Simultaneously they also accomplished the synthesis of (+)-pericosine B and (+)-pericosine C following the identical synthetic sequence but starting from D-ribose derived hemiacetal 499 [126].

### 6. NATURAL PRODUCTS OF ANIMAL ORIGIN

#### 6.1. Tricyclic Core of Solanoeclepin A

Hiemstra et al. utilized intramolecular [2+2] photocycloaddition of an allene butenolide 506 for compact tricyclic core 507, 508 of solanoeclepin A (509), a hatching agent of potato cyst nematodes [127]. This key allene butenolide was prepared from the allyl bromide 504 which in turn was prepared in four steps from the MBH adduct 503 obtained via the MBH reaction between benzyl butadienolate 502 and paraformaldehyde (Scheme 78).
6.2. Himanimide A

Basavaiah and co-workers developed a one-pot sulphonic acid-mediated procedure for the synthesis of unsymmetrical 3,4-disubstituted maleimide and maleic anhydride derivatives from the MBH adducts of α-keto esters and acrylonitrile. They extended this strategy for the synthesis of biologically active himanimide A (513) in 11.38% overall yield (Scheme 79) [128]. Subsequently, application of identical protocol on the MBH adducts of α-ketoesters and acrylate afforded a series of maleic anhydride. The 3-benzyl-4-phenyl maleic anhydride (515), prepared during the study is a natural compound isolated from Aspergillus nidulans (Scheme 80).

6.3. Leu- and Met-enkephalin Analogues

Leu-enkephalin (522) and met-enkephalin (523) are two endogenous peptide ligands towards the δ-opioid receptor isolated from brain tissue and are involved in a large number of physiological processes. Their roles in behaviour, neuroendocrinology and pain transmission are well documented. Negri et al. employed the MBH adduct (517) [129] of formaldehyde and tert-butyl acrylate to prepare two conformationally constrained analogues of leu-enkephalin and met-enkephalin to study their biological activities [130]. They first completed the synthesis of the N-terminus of the peptide by carbamate formation and two subsequent S_N1 reactions. Following, the C-terminus was synthesized by EDCI coupling with appropriate amino acid as outlined in scheme 81.

6.4. Pheromones

[2E]-Butyl-oct-2-enal (532) is an alarm pheromone component of the African weaver ant Oecophylla longinoda [131] and [2E]-2-tridecylheptadec-2-enal (533) is an unusual metabolite from the red alga Laurencia undulata and Laurencia papillosa [132]. Basavaiah and Hyma reported the synthesis of these important pheromones by using MBH reaction between aldehyde 524 or
536. Thus obtained was reduced with Pd/C to obtain racemic sitophilate male of the granary weevil in the MBH reaction with 1-propanal under ultrasound condition in the presence of DABCO (Scheme 81). Almeida’s groups have accomplished the synthesis of this compound using pentan-3-yl acrylate and methyl acrylate [133]. The respective cinnamate 530 and 531 were prepared via S_n2’ substitution reaction onto the acetates 528 and 529 with appropriate Grignard reagent. Subsequently, DI-BAL-H mediated reduction of the ester group reduction to alcohol followed by oxidation of hydroxyl group to formyl afforded the corresponding phoromones 532 and 533 (Scheme 82).

(±)-Sitophilate (536) is the aggregation pheromone produced by male of the granary weevil Sitophilus granaries [134]. Coelho’s and Almeida’s groups have accomplished the synthesis of this compound using pentan-3-yl acrylate (534) as the activated alkene in the MBH reaction with 1-propanal under ultrasound condition in the presence of DABCO (Scheme 83) [135]. The MBH adduct 535 thus obtained was reduced with Pd/C to obtain racemic sitophilate 536 in 81% yield.

In a different study Sá et al. used 2-methylbut-1-ol (537) as the electrophile in MBH reaction with methyl acrylate to obtain the MBH adduct 538 which was transformed to insect pheromone 541 via bromination, zinc promoted reduction and saponification steps (Scheme 84) [136].

Besides Das et al. were also able to synthesize five important insect pheromones which included (2E,4S)-2,4-dimethylhex-2-enoic acid, a mandibular-gland secretion pheromone of the male carpenter ant in the genus Camponotus, (+)-(S)-manicone (543) and (+)-(S)-normanicone (544), two mandibular-gland constituents of Manica ants, (+)-dominicalure-I (546) and (+)-dominicalure-II (547), two aggregation pheromones of the lesser grain borer Rhizoperthadominica (Scheme 85) [137]. Here too, the functionalization of the acid group of the MBH adduct 538 prepared from the
The presence of KOH yielded the potassium salt. Catalyzed carbonylation afforded a nitrile followed by treatment with ethyl chloroacetate. A Pd-Pfizer drug used for the treatment of neuropathic pain is synthesized by MBH adduct of ethyl and iso-propyl aldehyde. via chiral aldehyde 537 was the highlighting feature of their strategy for obtaining 544 and 545. Likewise, 548 and 549 were obtained via reaction of chiral pentan-2-ol with the alkenoic acids derived from the MBH adduct of ethyl and iso-propyl aldehyde.

7. SYNTHESIS OF DRUG MOLECULES

7.1. Pregabalin

The starting material 551 for pregabalin (555), an anticonvulsant drug used for the treatment of neuropathic pain is synthesized by Pfizer via MBH reaction between isobutyraldehyde 550 and acrylonitrile followed by treatment with ethyl chloroacetate. A Pd-catalyzed carbonylation afforded 552 which upon hydrolysis in the presence of KOH yielded the potassium salt 553. Asymmetric hydrogenation of 553 in the presence of a chiral Rh-catalyst ([([R,R]-Me-DuPHOS)Rh(COD)]-BF₄) gave the precursor 554 in 96.6% ee (Scheme 86) [138].

7.2. (+)-Efaroxan Precursor

Coelho et al. elegantly utilized the MBH adduct 557 prepared from 2-fluorobenzaldehyde and methyl acrylate for the straightforward, enantioselective synthesis of R-(+)-2-ethyl-2,3-dihydrofuran-2-carboxylic acid (562) in 8 steps. A LiMe₂Cu-mediated nucleophilic substitution reaction, Sharpless epoxidation and intramolecular cyclization for preparing the cyclic ether were some of the key steps in the synthesis (Scheme 87) [139]. Compound 562 is the direct precursor of R-(+)-efaroxan, used for the treatment of neu-
rododegenerative diseases (Alzheimer’s or Parkinson disease), migraine and type II (non-insulin dependent) diabetes.

They extended the approach to develop an asymmetric synthesis of both enantiomers of DFP analogues 573 and 574 from the epoxide precursor 569 (Scheme 88) [140].

7.3. LK-903

Das and co-workers reported an efficient and stereoselective synthesis of (E)-α-methylcinnamic acids in one-pot by reduction of the unmodified MBH adduct methyl-3-hydroxy-3-aryl-2-methylpropanoate (576) with I₂/NaBH₄. The protocol was extrapolated for the total synthesis of 1-(p-(myristyloxy)-α-methylcinnamoyl) glycerol, LK-903 (580), a highly active hypolipidemic agent by functional group transformation of the acid moiety (Scheme 89) [141].

7.4. Sordarin Core

Ciufolini et al. utilized the MBH adduct 583, prepared from the reaction between a typical aldehyde 556 and acrylonitrile, to obtain the ketone 586, which served as the useful building block for the preparation of analogues of the potent antifungal agent, sordarin 587. It was presumed that the exposure of the adduct 583 to TIP-SOTf induces the formation of the bis-trialkylsilyl derivative 584, which undergoes a spontaneous Diels-Alder reaction to furnish 585 as mixture of diastereomers (Scheme 90) [142].

7.5. Bupropion

Bupropion or [(+)α-4-butylamino 3-chloropropiophenone] is a potent inhibitor of dopamine reuptake with subtle noradrenergic reuptake. Bupropion is a typical antidepressant, which has been licensed by FDA to treat the smoker’s abstinence syndrome. Bupropion is administered in its racemic form, since it racemizes very quickly in the body when administered in its enantiomerically pure form. Coelho et al. used the MBH reaction to accomplish the total synthesis of (+)-bupropion in eight steps with an overall yield of 25%. In this approach they performed the MBH reaction of methyl acrylate with 3-chlorobenzaldehyde under sonication. Subsequently, the MBH adduct was transformed to the acylol derivative (591) which was utilized to prepare bupropion (Scheme 91) [143].
7.8. Tamiflu

Oseltamivir phosphate (Tamiflu), an orally effective antiviral drug, is reported to inhibit the neuraminidase enzyme of several influenza viral strains. Sudalai et al. reported an enantioselective route for the synthesis of tamiflu and (-)-methyl 3-epi-shikimate using Sharpless asymmetric epoxidation to initially prepare the epoxy alcohol 608 which was oxidized to aldehyde 609 (Scheme 94). A diastereoselective Barbier allylation reaction on 609 with the allyl bromide 238 prepared from the MBH adduct afforded the product 610 which was tailored further to arrive at a diene 611 [146]. A RCM reaction was performed on 611 to construct the cyclohexene core 612 of the molecule. The target compound was achieved via the aziridation route as reported earlier [147].

Recently, we also reported the synthesis of Corey’s tamiflu intermediate from N-Boc-L-serine methyl ester using MBH reaction as one of the key steps [148]. The N-Boc-L-serine methyl ester (616) was synthetically manipulated to the acetonide protected aldehyde 617 which was subjected to MBH reaction with ethyl acrylate under neat condition to generate the adduct 618. Thereafter, catalytic reduction of 618 followed by acylation via S_N2 displacement reaction afforded the diene 620. The RCM reaction of hydroxyl group elimination gave the Corey’s intermediate 622 in 22% overall yield (Scheme 95). Simultaneously, we utilized N-Boc-D-serine methyl ester to prepare the other isomer of the Corey’s tamiflu intermediate via identical route.

In addition, the Corey’s intermediate was utilized to synthesize GABA receptor inhibitor natural neurotoxin gabaculine as HCl salt (625) by simple saponification and Boc-deprotection (Scheme 96).

In addition, during the preparation of the manuscript Taylor and co-workers reported a novel synthesis of natural neurite outgrowth inducer (+)-neuchromenin using MBH reaction as one of the key steps [149].
Applications of Morita-Baylis-Hillman Reaction


Scheme 95.

Scheme 96.

8. CONCLUSION

In summary, the chemistry related to MBH adducts or their derivatives has made tremendous impact in the realms of synthetic natural product chemistry for accomplishing synthesis of a variety of natural products. Besides, employing the MBH chemistry in the scheme of events also allows construction of close analogues of the required natural products which provides a platform to develop structure activity relationship if the original compound has bioactivity. Moreover, the influence of MBH reaction on obtaining drugs/drug intermediate is also growing which is demonstrated by formulating simple routes to popular drug like Tamiflu. Although there has been formidable development in the area, it is envisaged that as the MBH adducts and their derivatives offer limitless opportunities, the synthetic chemists will be sufficiently motivated to keep on exploring new/alternate synthesis of natural products using this chemistry.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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ABBREVIATIONS

Ac = acetyl
Am = amyl
aq = aqueous

Boc = tert-butyloxycarbonyl
Cbz = benzyloxycarbonyl
c onc = concentrated
CSA = camphor sulphonic acid
d = day(s)
DABCO = diazabicyclo[2.2.2]octane
DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene
DBP = Di-n-butyl phthalate
DCB = dichlorobenzene
DDQ = 2,3-dichloro-5,6-dicyanobenzoquinone
d e = diastereomeric excess
DEAD = diethyl azodicarboxylate
DIBAL-H = diisobutylaluminium hydride
DIC = diisopropyl carbodimide
DIPEA = diisopropyl ethylamine
DIPt = diisopropyl tryptamine
DFP = difluorophosphate
DMA = dimethoxyacetamide
DMAP = 4-dimethyl aminopyridine
DME = 1,2-dimethoxyethane
DMF = N,N-dimethylformamide
DMP = Dess-Martin periodinane
DMSO = dimethylsulfoxide
dr = diastereomeric ratio
DTBMP = 2,6-Di-tert-butyl-4-methylpyridine
DYKAT = Dynamic kinetic asymmetric transformation
EDCI = N-ethyl-N-(3-dimethylaminopropyl)-carbodimide
ee = enantiomeric excess
E = Entgegen
NBS = normality
MW = microwave
Fmoc = Fluorenlymethoxy carbonyl chloride
h = hour(s)
hv = ultraviolet irradiation
HBTU = O-Benzotriazole-N,N,N',N'-tetramethyluronium hexafluoro-phosphate
Hex = hexyl
HFIPA = 1,1,1,3,3,3-Hexafluoropropylacrylate
HIV = human immunodeficiency virus
HMPA = hexamethylphosphoryl azide
HIVE = Horner-Wadsworth-Emmons
HQD = hydroxyquinuclidine
HMPA = hexamethylphosphoryl azide
ICD = isocupridine
EtOAc = ethyl acetate
IBX = 2-Iodoxybenzoic acid
HWE = Horner-Wadsworth-Emmons
IBX = 2-Iodoxybenzoic acid
ICD = isocupridine
ICSM = inhibitory concentration required for 50% inhibition
ICD = isocupridine
IMIDA = intramolecular Diels-Alder
Me = methyl
MEM = methoxyethoxymethyl
LDA = lithium diisopropylamide
LHMDA = lithium hexamethyldisilazide
MBH = Morita-Baylis-Hillman
m-CPBA = meta-chloroperbenzoic acid
Me = methyl
MEM = methoxyethoxymethyl
min = minute(s)
MOM = methylmethylene
Ms = mesyl (methanesulfonyl)
MS = molecular sieves
MW = microwave
N = normality
NBS = N-bromosuccinimide
NMM = N-methyl morpholine
NMO = N-methyl morpholine-N-oxide
NMP = N-methyl pyrrolidin-2-one
TF = trifluoromethane sulphonate
PCC = pyridinium chlorochromate
PDC = pyridinium dichromate
Pd/C = palladium on carbon
Ph = phenyl
PivOH = pivalic acid
PMB = para-methoxybenzyl
PPTS = pyridinium p-toluene sulphonate
PTSA = para-toluenesulphonic acid
Py = pyridine
rt = room temperature
RCM = ring closing metathesis
sec = secondary
S_N = nucleophilic substitution
TBAI = tetrabutyl ammonium iodide
TBAF = tetrabutyl ammonium fluoride
TBD = triazabicyclodecene
TBDMS = terti-butyl dimethyl sulfoxide
TBDPS = terti-butyl diphenyl sulfoxide
TBHP = terti-butyl hyperoxide
TBS = terti-butyl sulfoxide
TEMPO = 2,2,6,6-Tetramethylpiperidin-oxyl
tert = tertiary
TES = triethylsilane
TFA = trifluoroacetic acid
THF = tetrahydrofuran
TIPS = triisopropylsilylethyl
TMSET = 2-(trimethylsilyl)ethyl
tol = tolyl
TPAP = Tetrapropylammonium perruthenate
TBAB = tetrabutyl ammonium bromide
TPPTS = pyridinium toluenesulphonate
Z = Zussamen

REFERENCES

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