Asymmetric Catalysis

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Efficient Construction of the Clerodane Decalin Core by an Asymmetric Morita–Baylis–Hillman Reaction/Lewis Acid Promoted Annulation Strategy**

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Dedicated to Professor James S. Panek on the occasion of his 50th birthday.

The clerodane class of natural products are diterpenes that exhibit wide-ranging structural diversity.[1] Over 150 new bioactive clerodanes have been reported since 2002.[2] Of particular interest are asmarines A (**1**) and B (**2**)[3] and popolohuanone E (**3**),[4] members of this class of natural products that exhibit potent antiproliferative activity against several types of human-cancer-cell lines (Scheme 1).[5] Popolohuanone E is a topoisomerase II inhibitor,[4] whereas the biological target of asmarine A or B is not known. Given their biological activity and the prevalence of the structural motif they display, a general and efficient strategy towards the core structure of the clerodane would be attractive.

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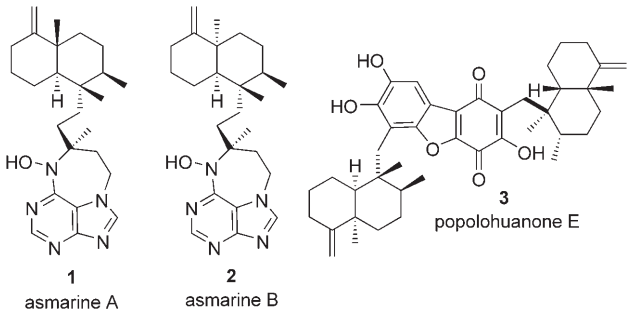
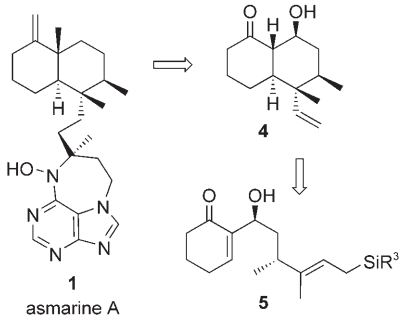


Scheme 1. Biologically active clerodane natural products.

Synthesis of the diterpene core structure has focused on elaboration of the Wieland–Miescher ketone.[6] Complementary approaches have elegantly utilized diastereoselective ring-annulation strategies towards substituted decalin structures; however, these approaches have mainly been racemic.[7] Recently, we reported the asymmetric Morita-Baylis-Hillman (MBH) reaction of cyclohexenone with aldehydes promoted by trialkyl phosphines and catalyzed by binaptholderived Brønsted acids.[8] We envisioned an asymmetric synthetic strategy toward the clerodane decalin core through a two-step ring-annulation procedure (Scheme 2).[9] The first

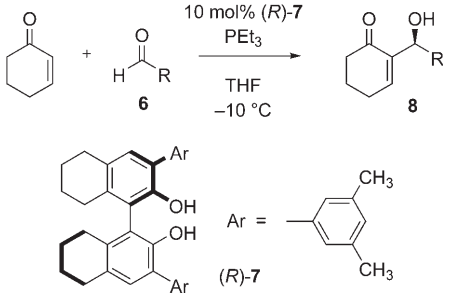


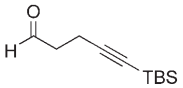
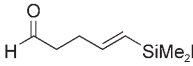
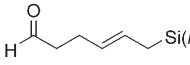
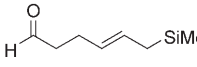
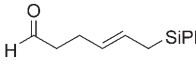
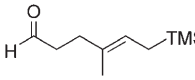
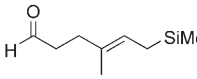
Scheme 2. Retrosynthetic analysis of asmarine A (**1**), thus illustrating the key MBH building block **5**.

step would be an asymmetric MBH reaction of cyclohexenone with an aldehyde functionalized with an appropriate nucleophile[10] followed by a Lewis acid promoted ring formation.[11] The ring-annulation strategy we chose was an intramolecular Hosomi–Sakauri reaction[12] that required the synthesis and use of aldehydes containing allyl silanes in the asymmetric MBH reaction. Herein, we report the construction of the clerodane decalin core through an asymmetric MBH reaction/Lewis acid promoted annulation strategy.

The strategy relies on two key experimental observations. First, the allyl silyl containing aldehyde must afford the MBH product with high enantioselectivity. Second, the enantiomeric excess of the product must be maintained during the ring-annulation process. We initially evaluated the scope of the MBH reaction of cyclohexenone with unsaturated silane containing aldehydes (Table 1). We found the Brønsted acid catalyzed phosphine-promoted MBH reaction conditions were mild enough to tolerate a variety of silane-containing aldehydes.[13]

Table 1: Brønsted acid catalyzed asymmetric MBH reactions.[a]



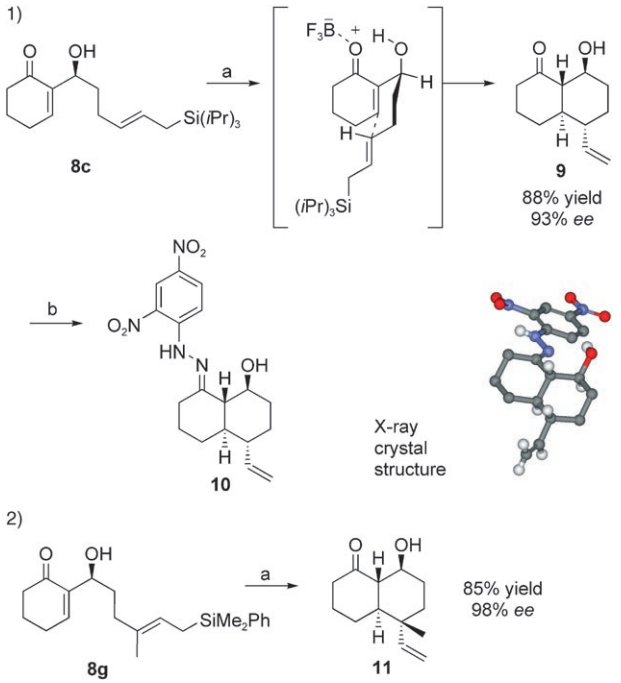
Entry	Aldehyde	Yield [%][b]	*ee*[c] [%]
1		**8a** (75)	86
2		**8b** (94)	98
3		**8c** (96)	93[d]
4		**8d** (80)	90
5		**8e** (75)	91[d]
6		**8f** (94)	93
7		**8g** (97)	98

[a] Reactions were run with **6** (1 mmol), cyclohexanone (2 mmol), PEt_3 (2 mmol), and (*R*)-**7** (0.1 mmol) in THF (1 M) at −10 °C for 48 h under argon followed by flash chromatography on silica gel. [b] Yield of the isolated product. [c] Determined by chiral HPLC analysis. [d] Enantiomeric excess of the major olefin isomer. TBS = tributyldimethylsilyl, TMS = trimethylsilyl.

We first considered alkynyl and vinyl silanes in the reaction (Table 1, entries 1 and 2). Although the general reaction conditions afforded the alkyne-containing product **8a** in only 86% *ee*, the vinyl silane containing aldehyde underwent a more selective reaction (98% *ee*). The MBH reaction conditions proved general for allyl silane containing aldehydes **6c–g** (Table 1, entries 3–7). The reaction of these aldehydes with cyclohexenone promoted by PEt_3 and 10 mol% of catalyst **7** in THF at −10 °C afforded the corresponding MBH products **8c–8g** in good yields (75–97%) and with high enantioselectivities (90–99% *ee*). The successful MBH reactions of this substrate class illustrated that acid-sensitive, multifunctional aldehydes of this type could be tolerated in the reaction. With the successful production of these MBH products, we began our investigation of the Lewis acid promoted ring annulation as a way to access the desired decalin ring system.

Experiments were carried out to determine the feasibility of a diastereoselective ring annulation of **8c**. A selection of Lewis acids ($BF_3{\cdot}OEt_2$, $[TiCl_4]$, $[Yb(OTf)_3]$, $[Sc(OTf)_3]$, and $MgBr_2$; OTf = triflate) were evaluated in the reaction for their ability to affect the intramolecular ring formation diastereo-

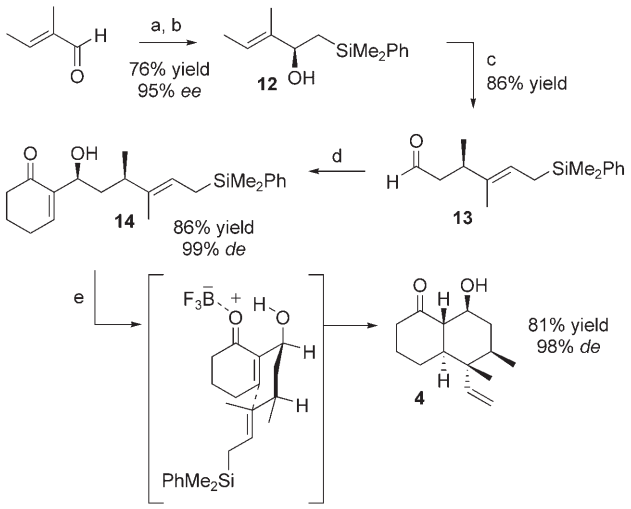
selectively and result in high yields while maintaining the enantiomeric excess during the reaction.[7a] Although many of these Lewis acids were capable of affecting ring formation, $BF_3{\cdot}OEt_2$ was found to be optimal for yield and chemoselectivity. Treatment of allyl silane **8c** with $BF_3{\cdot}OEt_2$ at −78 to −10 °C resulted in efficient ring formation to afford decalin **9** in 88 % yield of the isolated product as a single diastereomer (Scheme 3). The enantiomeric excess of the product was



Scheme 3. Ring-annulation reactions of allyl silane containing MBH products 1) **8c** and 2) **8g**. a) $BF_3{\cdot}OEt_2$, CH_2Cl_2, −78→−10 °C; b) dinitrophenylhydrazine, EtOH, RT. X-ray structure of **10**.

determined to be 93 % *ee* by chiral HPLC chromatography. The formation of the *trans* decalin bicylic ring structure was confirmed by X-ray crystallographic analysis of the corresponding dinitrophenyl hydrazone **10**. The observed selectivity can be rationalized by a chairlike transition state that places the secondary alcohol in an equatorial position. Protonation of the resulting enolate after the conjugate addition affords the thermodynamically favored *trans* decalin system. The reaction conditions using $BF_3{\cdot}OEt_2$ proved equally effective at promoting the ring annulation of allyl silane **8g**. The bicyclic product was formed in 85 % yield without a significant change in the enantiomeric excess. The formation of *trans* decalin was confirmed by an observed NOE interaction between the axial $-CH_3$ group and the axial methine hydrogen atom.

We next set out to construct the chiral aldehyde required for the synthesis of the clerodane core structure through the two-step asymmetric MBH reaction/Lewis acid promoted ring-annulation strategy. Our strategy for the synthesis of **13** relied on an asymmetric reduction followed by a stereoselective [3,3] sigmatropic rearrangement of the corresponding vinyl ether (Scheme 4).[14] The Gringard reaction of tiglic aldehyde with $ClMgCH_2SiMe_2Ph$ followed by oxidation of



Scheme 4. Synthesis of clerodane core **4**. a) 1. $ClMgCH_2SiMe_2Ph$, Et_2O, 0 °C; 2. IBX, EtOAc, 76 °C; b) (*R*)-Me-CBS (0.4 equiv), BH_3, THF, −50 °C; c) 1. $Hg(OAc)_2$ (0.028 equiv), $EtOCH{=}CH_2$, 35 °C; 2. chromatography on silica gel; d) cyclohexenone, PEt_3, (*R*)-**7** (0.1 equiv), THF, −10 °C, 48 h; e) $BF_3{\cdot}OEt_2$, CH_2Cl_2, −78→−10 °C. IBX = *o*-iodoxybenzoic acid. (*R*)-Me-CBS = (*R*)-methyl oxazaborolidine.

the resulting alcohol with IBX[15] in ethyl acetate afforded the ketone in 90 % yield. Asymmetric reduction of the unsaturated ketone with BH_3 catalyzed by the Corey (*R*)-Me-CBS catalyst[16] provided the requisite chiral allylic alcohol **12** in 95 % *ee*. Formation of the vinyl ether was carried out in refluxing ethyl vinyl ether and catalyzed by $Hg(OAc)_2$.[17] A stereoselective [3,3] sigmatropic rearrangement was found to proceed upon chromatography on silica gel to give the aldehyde in 85 % yield.[17] The asymmetric MBH reaction of aldehyde **13** with cyclohexenone using the Brønsted acid catalyst (*R*)-**7** afforded alcohol **14** in 86 % yield of the isolated product and 99 % *de*. The intramolecular Hosomi–Sakuari reaction using $BF_3{\cdot}OEt_2$ resulted in the clean formation of the desired clerodane core structure **4** in 81 % yield of isolated product and 98 % *de*. Based on our originally proposed transition state, the new methyl substituent in the six-membered transition state adopted an equatorial position that reinforced the chairlike transition state to yield *trans* decalin **4**. The substituents on the allyl silane work synergistically to produce high levels of diastereoselectivity; an approach that has previously been met with mixed success.[7c–d]

In summary, we have developed a general route to the clerodane diterpene core by using an asymmetric MBH/Lewis acid mediated ring-annulation process. We have expanded the scope of the asymmetric MBH reaction to include silane-containing aldehydes that can be utilized in synthesis. We have elaborated these MBH products into the *trans* decalin core by using an intramolecular Lewis acid promoted ring annulation. Utilization of this synthetic methodology in the synthesis of bioactive clerodanes is underway and will be reported in due course.

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