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Synthesis of (–)-Hebelophyllene E: An Entry to Geminal Dimethyl-Cyclobutanes by [2+2] Cycloaddition of Alkenes and Allenates

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Abstract

The first synthesis of hebelophyllene E is presented, along with assignment of its previously unknown relative configuration through synthesis of epi-ent-hebelophyllene E. Development of a catalytic enantioselective [2+2] cycloaddition of alkenes and allenates provides access to the required chiral geminal dimethylcyclobutanes. Key to its success is the identification of a novel oxazaborolidine catalyst which promotes the cycloaddition in high enantioselectivities with good functional-group tolerance (9 examples, up to 97:3 e.r.). Thus, a late-stage cycloaddition using a fully functionalized alkene, followed by a diastereoselective reduction allows a concise entry to this class of natural products.

Keywords

cycloaddition; enantioselectivity; natural products; small ring systems; total synthesis

Hebelophyllene E (**1**) is part of a small family of *cis*-fused caryophyllene-type sesquiterpenes which were isolated in the late 1990s from the ectomycorrhizal fungus *Hebeloma longicaudum*.^[1] Although this class of natural products has shown potential for nursery inoculation of conifer seedlings for better growth and survival in the fields, no synthetic access has been reported to date.^[2] Additionally, the authors of the isolation report were unable to determine the relative configuration of the C4 stereocenter,^[1c] and thus provided us with additional incentive for pursuing this total synthesis. Since previous methods to form geminal dimethylcyclobutanes in natural product synthesis^[3,4] do not provide access to the key β -cyclobutylacetate motif, development of such a method was required to ensure a concise synthesis. We intended to form the unusual *cis*-fused cyclobutane core by enantioselective alkene–allenate [2+2] cycloaddition^[5–8] followed by diastereoselective reduction (Scheme 1a).

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Conflict of interest

The authors declare no conflict of interest.

In the 1980s, Snider and co-workers reported an aluminum-promoted [2+2] cycloaddition between 2-methyl-2-butene and methyl allenolate to form dimethylcyclobutanes (Scheme 1b).^[9] The high level of regioselectivity presumably arises from an asynchronous cycloaddition in which the sigma bond between the most nucleophilic and the most electrophilic positions is formed first. To the best of our knowledge, this is the only example of successfully using a trisubstituted alkene for this type of transformation, and was reported to form the required dimethylcyclobutane motif. Because of the lack of an enantioselective version, this method was not a viable option for our synthesis. In 2015, our group identified a chiral oxazaborolidinium catalyst that was effective in promoting similar [2+2] cycloadditions and also allows excellent enantioinduction (Scheme 1b).^[10] However, trisubstituted alkenes were not compatible with these reaction conditions as low levels of selectivity were observed. Herein, we disclose our results on overcoming these limitations by catalyst optimization^[11] with a particular emphasis on prenylated substrates (Scheme 1c). Since more than 600 of the approximately 2300 known cyclobutene-containing-natural products comprise geminal dimethyl substitution, development of such a method does not only serve this particular synthesis, but is of general utility.^[12]

We initiated our studies by examining the cycloaddition of benzyl allenolate (**2**) and a triisopropylsilyl (TIPS) protected homoprenyl alcohol (**3a**) as a model alkene (Table 1). In agreement with our previous observations, the oxazaborolidine catalyst **4a** furnished the cyclobutane **5a** in modest enantioselectivity and poor *E/Z* selectivity (entry 1). Whereas alteration of the boroaryl substitution (entry 2–6) had a noticeable influence on the *E/Z* selectivity (e.g. entry 5), enantiomeric selectivities remained mostly unchanged. Examination of the backbone Rgroups resulted in a decrease of *E/Z* selectivity and enantioselectivity (compare entries 6 and 7). Based on this observation the boroaryl substitution of **4a** and the backbone Rgroup of **4g** were merged to reverse the *E/Z* selectivity and favor the *Z* isomer. To our delight, the catalyst **4h** also led to a significant increase in enantioselectivity (entry 8). Lowering the temperature to 4°C while extending the reaction time allowed 35:65 *E/Z* selectivity and excellent enantioselectivity for the major *Z*-configured isomer (entry 9). It should be noted that the pure *Z*-cyclobutane (*Z*)-**5a** could be isolated in 53% yield by means of flash column chromatography. Small amounts of the regioisomer and ene-product were always formed in the cyclo-addition (ca. 5%) and coeluted with the minor *E*-configured isomer.

Having identified a catalyst to perform the key reaction in our synthesis with high enantioselectivity, we investigated a selected substrate scope (Scheme 2). Functional groups such as silyl ether, ester, ketone, and benzyl ether were well tolerated [products (*Z*)-**5b–e**]. High chemoselectivity for the trisubstituted alkene in the presence of a terminal alkene was observed [(*Z*)-**5f**], and turned out to be essential for the synthesis of hebelophyllene E (**1**). Sterically smaller groups [e.g., product (*Z*)-**5g**, R = Me] resulted in lower *E/Z* selectivity and therefore lower yield upon isolation as the pure *Z* isomer, whereas bulky groups led to increased *E/Z* selectivity of up to 76:24 [product (*Z*)-**5e**, R = C(CH₃)₂OBn].

One unforeseen challenge we faced was achieving *cis*-selective reduction after forming the cyclobutane ring—as we discovered in the following investigation, *trans*-configured cyclobutanes are generally the major products. We started investigating the reduction on the

model system (*Z*)-**5a**, which was easily synthesized on scale. Our results are summarized in Table 2. Crabtree's catalyst resulted in completely selective formation of *trans*-**6** (entry 1). It is proposed that allylic strain (see proposed model in Table 2) leads to a puckered conformation in which the R group preferentially adopts a pseudoaxial conformation. As a result, favored attack occurs from the convex face.^[13] Magnesium in methanol, which usually furnishes the thermodynamically more stable product, also resulted in the *trans*-product as the major component (entry 2). When catalytically generated L_nCuH was used as the reductant (entries 3 and 4), higher yields and less pronounced *trans*-selectivity were observed.^[14] To overcome the selectivity issue, we turned to chiral ligands on copper to override the inherent substrate control. Indeed, racemic 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP) showed different selectivity compared to *R*-BINAP, thus making us confident in this approach (entries 5 and 6). A careful screening of ligands (see the Supporting Information for details) finally identified the Josiphos-type ligand **7** as a good source of induction switching the selectivity in favor of isomer *cis*-**6** (entry 7).^[15] To confirm the ligand control, the ligand *ent*-**7** was used, thus giving the expected *trans*-product as the major component in good yield (entry 8). A decrease in the temperature to -78°C, resulted in an increase in *cis*-selectivity as the cyclobutane *cis*-**6** was obtained in 85% yield and 80:20 diastereomeric ratio (d.r.; entry 9).

Confident that the functional-group tolerance of the reaction (Scheme 2) would allow us to pursue a more concise route to **1**, we initiated the synthesis of the fully functionalized alkenes **3h** and **3i** from known^[16] acyloin *rac*-**3f**, which was easily accessible on decagram scale (Scheme 3). Wessjohann and co-workers reported^[16] a kinetic resolution of *rac*-**3f** using amano lipase PS from *Burkholderia capacia*, which worked smoothly on gram-scale to provide both the starting material and product in greater than 99:1 e.r. Since the stereochemistry at C4 is unknown, access to both diastereomers of the alkene (**3h** and **3i**) was necessary. Hence, we attempted to control the approach of the vinyl Grignard reagent based on the polar Felkin-Anh model.^[17] We found that benzoyl (Bz) protection of the alcohol **3g** was beneficial for two reasons: 1) It showed very high Felkin-Anh control when treated with vinylmagnesium bromide in THF, and 2) It allowed direct removal of the protecting group by simply using excess Grignard reagent. After acetone protection using 2,2-dimethoxypropane (2,2-DMP) and *p*-toluenesulfonic acid (*p*-TsOH), the alkene **3h** could be purified by flash column chromatography and was isolated in greater than 99:1 d.r. and 59% yield over three steps. The relative configuration was proven by nuclear Overhauser effect (nOe) correlation while the absolute configuration was confirmed by comparing the intermediate diol to known literature data (see the Supporting Information for further details).^[18]

We originally thought to form the alkene **3i** by protecting **3g** with an established protecting group suited for chelation. To circumvent these stepwise protecting procedures, we considered a more direct approach starting from the enantiopure acetate **3f**, which is conveniently formed in the resolution (Scheme 3). After optimization, we found that the ester group itself was capable of chelation under ether-free conditions (note that dichloromethane was uniquely effective as a solvent) to give the Cram-chelate^[19] product in good selectivity (82:18). As before, utilizing excess vinylmagnesium bromide allowed direct

removal of the acetate and **3i** was isolated after acetonide protection in greater than 99:1 d.r. and 59% yield over both steps.

With the two alkenes in hand, each were subjected to the [2+2] cycloaddition conditions. Since **1** contains an *S* configuration at C1, the catalyst *ent*-**4h** was used (Scheme 4). We noticed a pronounced matched/mismatched scenario between the catalyst and the nature of the alkene's proximal stereo-center: While the alkene **3h** and catalyst *ent*-**4h** resulted in sluggish reaction and yields around 10%, **3i** reacted without complication in the [2+2] cycloaddition and (*Z*)-**5i** was isolated in 52% yield in greater than 99:1 e.r. and greater than 99:1 d.r. It is worth mentioning that the cycloaddition required four equivalents of alkene, slightly lower temperature, and higher catalyst loading^[20] to ensure high conversion. However, excess alkene can be recovered in 90–95% yield and reused in the cycloaddition. Fortunately, the succeeding reduction using matched ligand *ent*-**7** afforded the cyclobutane **8** with a high (89:11) d.r. value and excellent yield.

After deprotection of *cis*-**8** with trifluoroacetic acid (TFA), the incorrect relative configuration from the required matched cycloaddition, could be corrected by an oxidation/reduction sequence, thus providing the diol **9** in 69% yield and 71:29 diastereoselectivity after three steps (Scheme 4). Saponification followed by lactonization using the Steglich protocol^[21] delivered the lactone **10** in 94% yield. After trimethylsilyl (TMS) protection of the tertiary alcohol, the lactone was deprotonated using lithium hexamethyldisilamide (LiHMDS) and the respective enolate quenched with methyl iodide in greater than 20:1 diastereoselectivity. Upon work-up with HCl the TMS group was released and hebelphyllene E (**1a**) was isolated in 50% yield over the two steps (the minor isomer from the Zn(BH₄)₂ reduction was easily separated at this stage). All analytical data of the synthetic sample including optical rotation were in agreement with the reported data of the natural product.^[1c]

To confirm the relative configuration of C4, we also synthesized *epi-ent*-hebelphyllene E (**1b**) starting from the alkene **3h** and the respective matched catalyst **4h** (Scheme 4). The synthesis proceeded in 12% yield over nine steps using a closely related sequence as the one for hebelphyllene E (**1a**; see the Supporting Information for details). To our delight, the spectra of *epi-ent*-hebelphyllene E (**1b**) were in stark disagreement with those from the natural product. We also confirmed the relative configuration of all other stereo-centers by two-dimensional NMR analysis (see the Supporting Information for details), which allows us to confidently propose the depicted structure **1a** as the structure of hebelphyllene E.

In summary, the first synthesis of the sesquiterpene hebelphyllene E was accomplished and the relative configuration of the side-chain was assigned. Moreover, access to the *cis*-fused geminal dimethylcyclobutane core was achieved through development of a [2+2] cycloaddition involving a fully functionalized alkene and founded on the identification of a novel oxazaborolidine catalyst. Given the number of isolated geminal dimethylcyclobutane natural products, this method itself should be useful for future synthetic efforts in the field of cyclobutane natural product synthesis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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a) Retrosynthetic analysis

b) Prior work

Snider (1980):

Brown (2015):

c) This work

Scheme 1.

Retrosynthetic analysis and work on the key [2+2] cyclo-addition. Tf = trifluoromethanesulfonyl.

Scheme 2.

Substrate scope. [a] Yield of the isolated pure *Z* isomer. [b] Yield of combined cycloaddition products determined by ¹H NMR of the crude reaction mixture utilizing a calibrated internal standard. [c] ds = diastereomer. TBS = *tert*-butyldimethylsilyl.

Scheme 3.

Synthesis of both diastereomers of the desired alkene. Bz= benzoyl, DCC=1,3-dicyclohexylcarbodiimide, DMAP=4-(*N,N*-dimethylamino)pyridine, DMP =Dess—Martin periodinane.

a) Synthesis of Hebelophyllene E

b) Synthesis of *epi-ent*-Hebelophyllene E **Scheme 4.**Synthesis of Hebelophyllene E (**1a**) and *epi-ent*-Hebelophyllene E (**1b**).

HMDS=hexamethyldisilazide, TMS=trimethylsilyl.

Table 1

[2+2] Cycloaddition: Reaction optimization.

Entry	R	Ar	Yield [%]	[a]	E/Z	[a]	er	[b]
1	Ph	2-CF ₃ -4-Cl-C ₆ H ₃ (4a)	89		49:51		81:19	
2	Ph	4-CF ₃ -C ₆ H ₄ (4b)	87		70:30		76:24	
3	Ph	3,5-(CF ₃) ₂ -C ₆ H ₃ (4c)	79		77:23		80:20	
4	Ph	2,3-(Cl) ₂ -C ₆ H ₃ (4d)	68		81:19		82:18	
5	Ph	4-F-1-naphthyl (4e)	72		82:18		85:15	
6	Ph	4-CF ₃ -2-CH ₃ -C ₆ H ₃ (4f)	70		72:28		83:17	
7	3,5-(CF ₃) ₂ -C ₆ H ₃	4-CF ₃ -2-CH ₃ -C ₆ H ₃ (4g)	87		66:34		79:21	
8	3,5-(CF ₃) ₂ -C ₆ H ₃	2-CF ₃ -4-Cl-C ₆ H ₃ (4h)	79		40:60		91:9	
9	[c]		86 (53)	[d]				

[a] Determined by ¹H NMR analysis of the crude reaction mixture utilizing a calibrated internal standard.

[b] Determined by HPLC analysis using a chiral column; reported e.r. of the major isomer.

[c] Reaction was run at 4°C for 48 h.

[d] Yield of isolated pure (*Z*)-**5a** given within parentheses.

Table 2

Conjugate Reduction: Optimization and model.

Entry	Conditions	Yield [%] ^[a]	<i>trans/cis</i> ^[a]
	Crabtree's catalyst, ^[b] H ₂ (CH ₂ Cl ₂)RT, 16h		
2	Mg (MeOH) RT, 16 h	53	86:14
3	SIMesCuCl, ^[c] NaOtBu, PhSiH ₃ , tBuOH (THF) RT, 3 h	83	81:19
4	SIPrCuCl, ^[c] NaOtBu, PhSiH ₃ , tBuOH (THF) RT, 3 h	87	65:35
5	<i>rac</i> -BINAP, Cu(OAc) ₂ , ^[c] PhSiH ₃ , tBuOH (THF) RT, 3 h	26	90:10
6	<i>R</i> -BINAP, Cu(OAc) ₂ , ^[c] PhSiH ₃ , tBuOH (THF) RT, 16 h	79	71:29
7	7, Cu(OAc) ₂ , ^[c] PhSiH ₃ , tBuOH (THF) RT, 16 h	88	35:65
8	<i>ent</i> -7, Cu(OAc) ₂ , ^[c] PhSiH ₃ , tBuOH (THF) RT, 16 h	94	92:8
	7, Cu(OAc) ₂ , ^[c] PhSiH ₃ , tBuOH (THF) – 78 ° C, 2h		

^[a] Determined by ¹H NMR analysis of the crude reaction mixture utilizing a calibrated internal standard.

^[b] 2.5 mol% used.

^[c] 0 mol% used. THF=tetrahydrofuran.