Efficient Enantioselective Total Synthesis of (+)-Helianane

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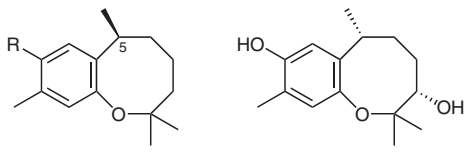
Received 1 February 2011

Abstract: The enantiocontrolled total synthesis of (+)-helianane, a marine-derived heterocyclic sesquiterpene, has been accomplished with an efficient chirality transfer during the Me_3Al-mediated aromatic Claisen rearrangement and a ring-closing metathesis as the key steps. The absolute structure of the natural product has been firmly established by total synthesis.

Key words: metathesis, total synthesis, terpenoids, Claisen rearrangement, helianane

The sesquiterpene helianane (**1**)[1] was isolated from the sponge *Haliclona fascigera* by Crews et al. Its structure, which was elucidated by extensive NMR studies, revealed that helianane possesses a tetrahydrobenzoxocine skeleton with a tertiary stereogenic center at the benzylic position. The absolute configuration at the C5 stereogenic center was deduced to be *S* by a preliminary assignment based on an approximate relationship between the absolute stereochemistry of the C–CH_3 group and the *d*/*l* optical rotation in aromatic bisabolene derivatives.[2] Although there have been no reports on possible biological activity of the natural product, the related chlorinated congener **2**, isolated from the sponge *Spirastrella hartmani* along with the bromo analogue **3**, has been shown to exhibit in vitro cytotoxic activity.[3] Because of its simple and interesting structural features, the racemic **1** has been the subject of five reported total syntheses;[4] however, no enantioselective synthesis has ever been accomplished. During the course of our synthetic studies on the sunflower-derived helianane sesquiterpenes,[5] we published the enantioselective total synthesis of heliannuol A (**4**), which has a structure similar to that of **1**, and we established its absolute structure by total synthesis.[6] Here we describe the first enantioselective total synthesis of helianane (**1**), which allowed the confirmation of the absolute structure (Figure 1).



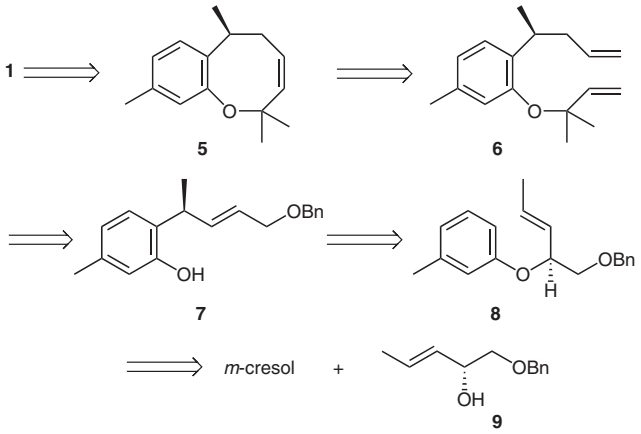
helianane (**1**) R = H
2 R = Cl
3 R = Br

heliannuol A (**4**)

Figure 1 Structures of helianane and heliannuol A

SYNLETT 2011, No. 8, pp 1171–1173
Advanced online publication: 20.04.2011
DOI: 10.1055/s-0030-1260532; Art ID: U01311ST

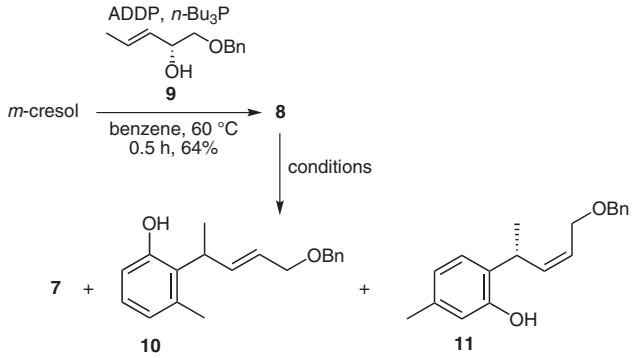
Our strategies for the synthesis of helianane (**1**) are illustrated in Scheme 1. For the synthesis of **1** we chose the dihydrobenzoxocine **5** with a stereogenic center at C5 as the penultimate intermediate, which can be converted into **1** by hydrogenation. The eight-membered heterocycle fused to the aryl ring would be assembled by ring-closing metathesis of the diene **6**, which would be prepared from the phenol **7** by Pd-catalyzed dimethylallyl etherification.[6,7] For the key construction of the tertiary stereogenic center at the benzylic position, we planned to use a substrate-controlled chirality transfer in the Claisen rearrangement[8,9] of the allyl aryl ether **8** prepared from *m*-cresol and *R*-(*E*)-1-(benzyloxy)pent-3-en-2-ol (**9**)[10] by the Mitsunobu coupling[11] (Scheme 1).



Scheme 1 Retrosynthetic analysis

The Mitsunobu reaction between *m*-cresol and the alcohol **9**, derived from *R*-(–)-benzyl glycidyl ether in two steps, in the presence of 1,1-(azodicarbonyl)dipiperidine (ADDP)[12] and *n*-Bu_3P proceeded in 64% yield to give the ether **8** (>99% ee; by HPLC analysis using a Chiralcel AD column).[13] The key Claisen rearrangement of **8** was examined, and the results are shown in Table 1. On heating a solution of **8** in *N*,*N*-dimethylaniline at 210 °C for 1.5 hours,[9a] a chromatographically separable mixture of the desired phenol (*S*)-**7** was obtained in 50% yield in enantiomerically pure form (determined by HPLC analysis using a Chiralcel AD column), along with the regioisomer **10** (26%, entry 1) Treatment of a solution of **8** in dichloroethane with 10 mol% of $Eu(fod)_3$[9b] at 90 °C for 40 hours gave a mixture of **7** (>99% ee) and **10** in 71% and 21% yield, respectively (entry 2). The optimized reaction conditions call for 3 equivalents of Me_3Al[14] in hexane at room temperature for 0.5 hours; the requisite **7** was obtained in

Table 1 Results of the Claisen Rearrangement of Compound **8**

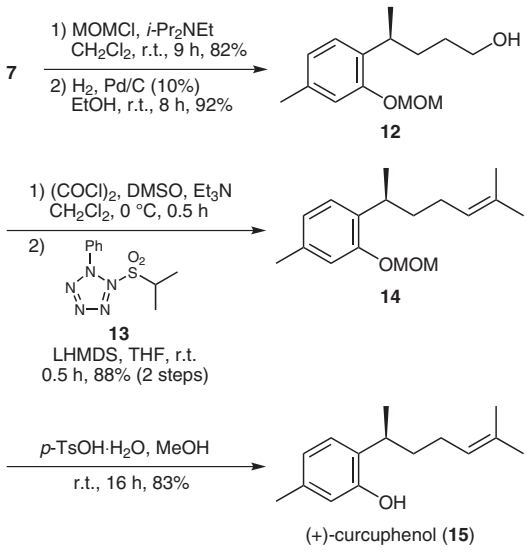


Entry	Conditions	Yield (%), ee (%)[a]		
		7	**10**	**11**
1	*N*,*N*-dimethylaniline, 210 °C, 1.5 h	50 (>99)	26	–
2	$Eu(fod)_3$ (10 mol%), DCE, 90 °C, 40 h	71 (>99)	21	–
3	Me_3Al (3 equiv), hexane, r.t., 0.5 h	84 (>99)	11	5

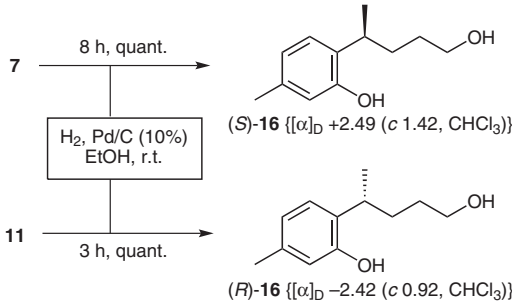
[a] HPLC (Chiracel AD column).

84% yield (>99% ee), together with **10** (11%) and the *Z*-isomer **11** (5%) with the *R* configuration at the future C5 (entry 3).

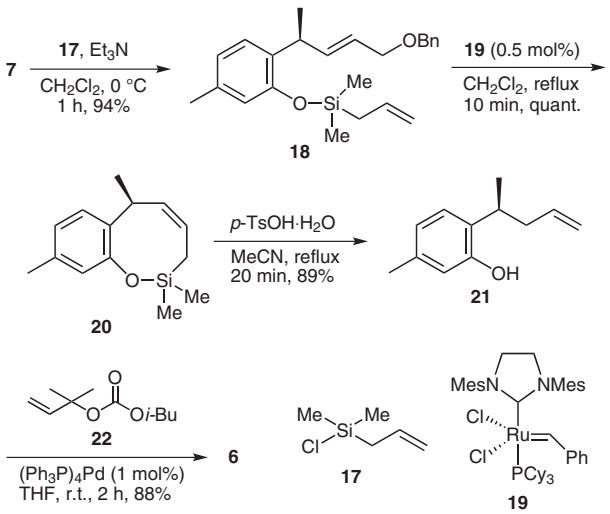
The absolute configuration of the stereogenic center of **7** was determined to be *S* by the conversion into curcuphenol (**15**).[2b,c,15] Thus, sequential protection of the phenolic hydroxyl as the methoxymethyl (MOM) ether and hydrogenation produced the alcohol **12**, which was oxidized under Swern conditions, and the resulting aldehyde was converted into the alkene **14** by the Julia–Kocienski olefination.[16] Finally, this compound was hydrolyzed with acidic conditions to give **15**, the spectral properties and optical rotations of which were identical to those of the natural (+)-curcuphenol (Scheme 2) {$[\alpha]_D$ +25.8 (*c* 0.39, $CHCl_3$); lit.[2b] $[\alpha]_D$ +24.6 ± 2; lit.[15] $[\alpha]_D$ +29.1 (*c* 3.13, $CHCl_3$)}.



Scheme 2



Scheme 3



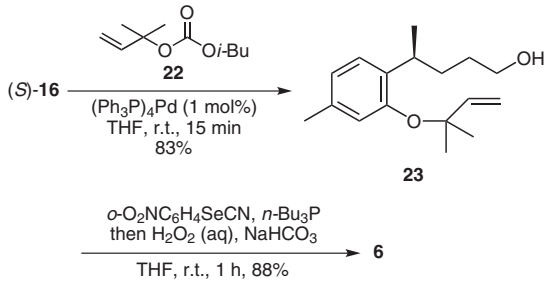
Scheme 4

As for the absolute structure of **11**, independent hydrogenation of **7** and **11** gave the phenolic alcohols (+)-**16** and (–)-**16**, respectively; thus the absolute configuration at the future C5 position in **11** was established to be *R* (Scheme 3).

The phenol **7** thus prepared was treated with allylchlorodimethylsilane (**17**) and triethylamine to give the silyl ether **18**, which was subjected to the ring-closing metathesis using the Grubbs second-generation catalyst **19** (0.5 mol%)[17] to yield quantitatively the eight-membered silyl ether **20**. Upon exposure to PTSA in refluxing acetonitrile, **20** underwent protodesilylation[18] to give the phenol **21** in 89% yield. Treatment of **21** with the mixed carbonate **22** in the presence of catalytic $(Ph_3P)_4Pd$ provided the diene **6** in 88% yield (Scheme 4).

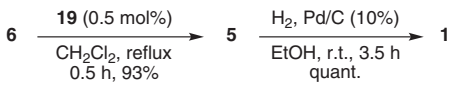
Alternatively, the diene **6**, the substrate for the ring-closing metathesis, was prepared starting from (*S*)-**16**, which was derived by hydrogenation of **7**, in two steps. Palladium-catalyzed chemoselective allylation of **16** provided the alcohol **23**, which was exposed to the dehydration protocol of the Nishizawa–Grieco[19] to give **6** efficiently (Scheme 5).

The requisite diene **6** then was treated with the Grubbs second-generation catalyst **19** (0.5 mol%) in refluxing dichloromethane to give the dihydrobenzoxocine **5** in 93% yield. Finally, hydrogenation over 10% Pd/C fur-



Scheme 5

nished the synthetic helianane (**1**)[20] quantitatively. All spectral data for the synthetic material were identical to those published,[1,4d] including the sign of the optical rotation[1] (Scheme 6).



Scheme 6

In summary, we have completed the first enantiocontrolled total synthesis of helianane using a chirality transfer that occurred with high selectivity during the Me_3Al-mediated Claisen rearrangement for the construction of the C5 stereogenic center and an efficient ring-closing metathesis for the construction of the basic carbon framework as the key steps in a longest linear sequence of seven steps from *m*-cresol with an overall yield of 34%. In addition, the absolute configuration at the C5 stereogenic center was firmly established by this total synthesis to be *S*, which had been proposed by Crews.[1] The synthetic route developed here is general and efficient and could also be applied to the syntheses of other related natural products.

Acknowledgment

We thank SANYO FINE Co. Ltd. for providing *R*-(–)-benzyl glycidyl ether. This work was supported financially by a Grant-in-Aid for the Program for Promotion of Basic and Applied Research for Innovation in the Bio-oriented Industry (BRAIN).

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(20) **Analytical Data for Helianane (1)**
$[\alpha]_D$ +24.0 (*c* 2.28, CH_2Cl_2) {Lit.[1] $[\alpha]_D$ +8.0 (*c* 1.01, CH_2Cl_2)}. IR (neat): 2973, 2926, 1456, 1382, 1256, 1138 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.06 (d, *J* = 8.0 Hz, 1 H), 6.88 (d, *J* = 8.0 Hz, 1 H), 6.71 (d, *J* = 1.5 Hz, 1 H), 3.19 (br s, 1 H), 2.27 (s, 3 H), 1.78–1.70 (m, 1 H), 1.62–1.56 (m, 1 H), 1.52 (m, 2 H), 1.46–1.32 (m, 2 H), 1.41 (s, 3 H), 1.28 (s, 3 H), 1.25 (d, *J* = 7.0 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.0, 138.8, 135.3, 125.8, 125.8, 124.9, 80.9, 39.7, 38.1, 31.5, 29.2, 26.7, 21.9, 21.2, 20.9. ESI-HRMS: *m/z* calcd for $C_{15}H_{22}ONa$ $[M^+ + Na]^+$: 241.1568; found: 241.1577.