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Total Syntheses of Both Enantiomers of Sarcophytols A and T Based on Stereospecific [2,3]Wittig Rearrangement

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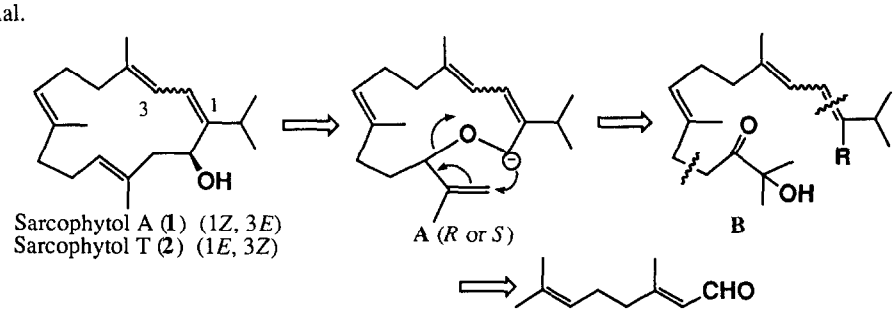
Abstract: Both enantiomers of sarcophytols A (**1**) and T (**2**), cembranolide diterpenes isolated from a soft coral, were synthesized from a common chiral intermediate, obtained by baker's yeast reduction, using a stereospecific [2,3]Wittig rearrangement as the key step.

Sarcophytols are cembrane-type diterpenes isolated from the soft coral, *Sarcophyton glaucum*, and have a conjugated dienol structure on a 14-membered ring as a common structural feature.[1] All geometrical isomers of the diene part have been found in the same soft coral, namely sarcophytols A (1*Z*, 3*E*),[1a] F (1*E*, 3*E*),[1d] N (1*Z*, 3*Z*),[1c] and T (1*E*, 3*Z*),[1f] together with further oxygenated congeners.[1b, 1d] Among them, sarcophytol A (**1**) has attracted the most attention because of its strong inhibitory activity against tumor promoters[2] and it has already been synthesized by two groups.[3]

In this communication, we would like to report a new type of synthesis of sarcophytol A (**1**) and also sarcophytol T (**2**) as well as their enantiomers. The retrosynthetic route is briefly shown below. The two key steps in our synthesis are the stereospecific [2,3]Wittig rearrangement of chiral bis-allyl ether **A**, which allows us to, simultaneously, construct the macro-carbocycle and introduce the 14-hydroxyl group and the enantioselective baker's yeast reduction [4] of an α-hydroxy ketone such as **B** which is accessible from geranial.



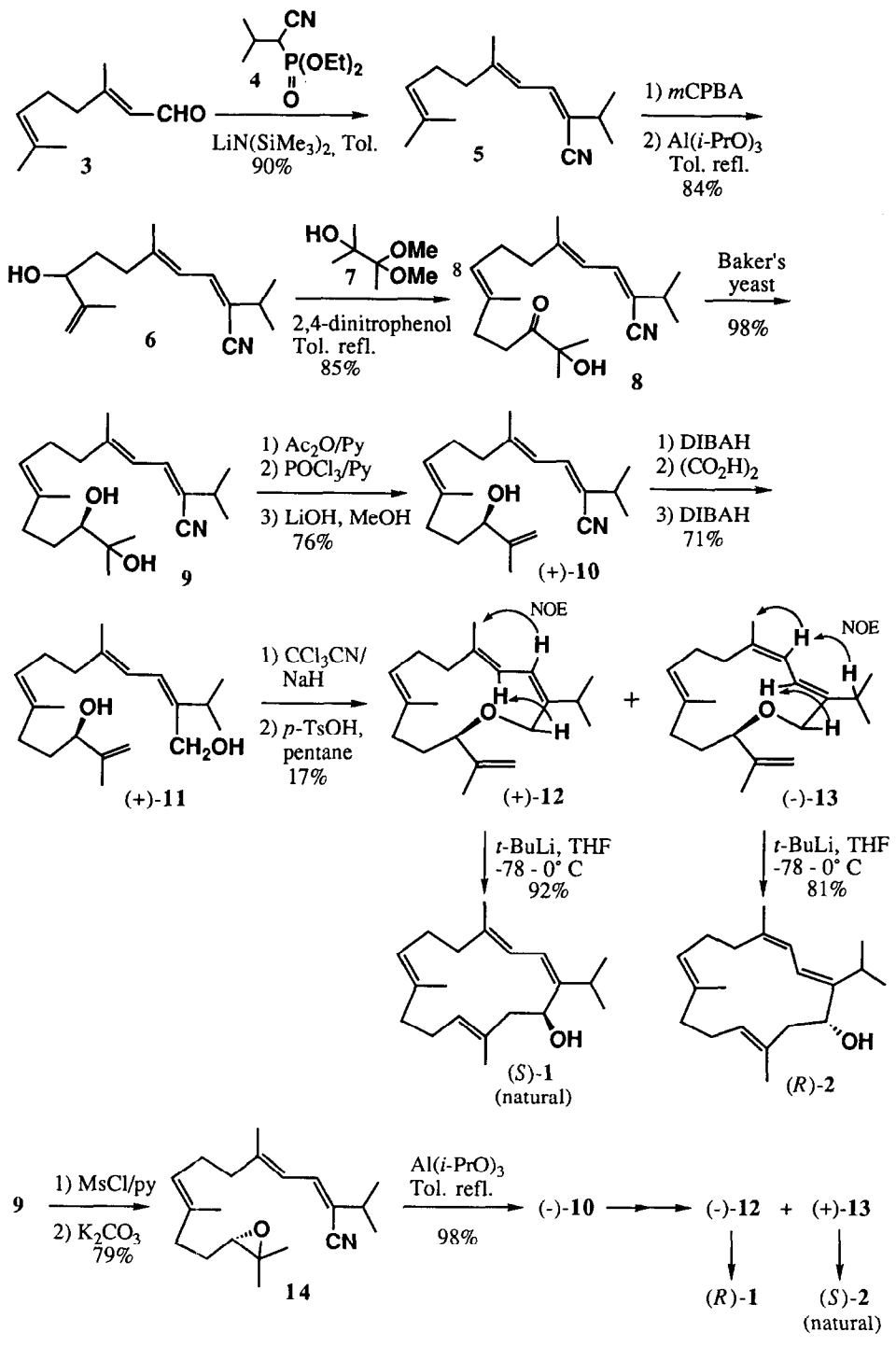
Sarcophytol A (**1**) (1*Z*, 3*E*)
Sarcophytol T (**2**) (1*E*, 3*Z*)

A (*R* or *S*)

B

Geranial (**3**)

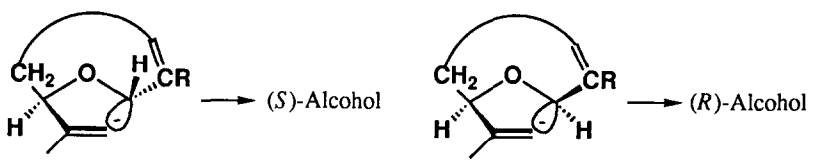
Horner-Emmons olefination of geranial (**3**) using the cyanophosphonate **4** yielded the *Z*-olefin **5** in high selectivity.[3a] The terminal double bond was selectively epoxidized and then the epoxide-ring was opened to


CN
P(OEt)2
O
4
CHO
3
LiN(SiMe3)2, Tol.
90%
5
CN
1) mCPBA
2) Al(i-PrO)3
Tol. refl.
84%
HO
6
CN
HO
OMe
7
OMe
8
2,4-dinitrophenol
Tol. refl.
85%
O
CN
OH
8
Baker's
yeast
98%
OH
CN
OH
9
1) Ac2O/Py
2) POCl3/Py
3) LiOH, MeOH
76%
OH
CN
(+)-10
1) DIBAH
2) (CO2H)2
3) DIBAH
71%
OH
CH2OH
(+)-11
1) CCl3CN/
NaH
2) p-TsOH,
pentane
17%
NOE
H
H
O
H
(+)-12
+
NOE
H
H
H
O
H
(-)-13
t-BuLi, THF
-78 - 0° C
92%
OH
(S)-1
(natural)
t-BuLi, THF
-78 - 0° C
81%
OH
(R)-2
9
1) MsCl/py
2) K2CO3
79%
O
CN
14
Al(i-PrO)3
Tol. refl.
98%
(-)-10
(-)-12
+
(+)-13
(R)-1
(S)-2
(natural)

afford the allylic alcohol **6**. Thus obtained **6** was subjected to Claisen rearrangement using the acetal **7** in refluxing toluene. The reaction proceeded in high yield to give rise to the α-hydroxy ketone **8** with 8*E*-double bond. The ketone **8** was then reduced with baker's yeast.[5] The absolute configuration of the diol **9**, $[\alpha]_D$ +20.0°, obtained in 98% yield was determined to be *R* on the basis of its CD spectrum [Δε; -11.7 (307 nm)] in the presence of $Eu(fod)_3$.[6] Acetylation of **9** and subsequent dehydration, followed by hydrolysis afforded the allylic alcohol (+)-**10** ($[\alpha]_D$ +7.3°), the optical purity of which was determined as 98% ee by HPLC analysis using a chiral column. The cyano-group in (+)-**10** was converted into a primary alcohol by means of a DIBAH reduction and then ether-ring formation was examined. However, attempts to convert the primary hydroxyl group of (+)-**11** into a halogen or sulfonate always resulted in the formation of a mixture of conjugated trienes formed by simple elimination. After many tries, we succeeded in synthesizing the cyclic ether by converting the primary hydroxyl group into a trichloroacetimidate followed by acid treatment,[7] although the yield was not quite satisfactory. The product was a mixture of two ethers in a ratio of 2:3. NOE experiments (indicated by arrows) indicated that one of the products (minor) was the desired ether (+)-**12**, retaining the geometry of conjugated diene, but in the other, (-)-**13**, the geometry of both double bonds was inverted. The crucial step of this synthesis, [2,3]Wittig rearrangement of (+)-**12** using *t*-BuLi in THF at -78°C, took place cleanly to yield natural-type sarcophytol A [(*S*)-**1**], $[\alpha]_D$ +203.2° (natural[3a] +228°); 91.4% ee by HPLC analysis, in 92% yield. Surprisingly, similar treatment of isomeric ether (-)-**13** with *t*-BuLi resulted in reverse chirality transfer giving unnatural-type sarcophytol T [(*R*)-**2**], $[\alpha]_D$ +4.5° (natural[1e]; -12°); 98% ee by HPLC analysis, in 81% yield.

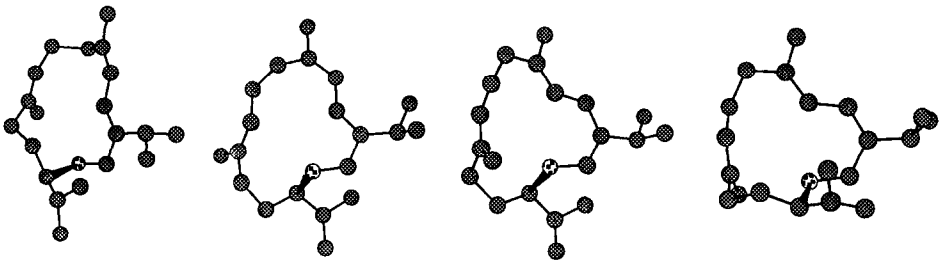
For the synthesis of natural-type sarcophytol T, the diol **9** was converted in two steps into the epoxide **14**, from which allylic alcohol (-)-**10** ($[\alpha]_D$ -6.9°) was prepared. By the same procedure as described above, (-)-**10** was converted into ethers (-)-**12** and (+)-**13**. [2,3]Wittig rearrangement of (+)-**13** and (-)-**12** yielded natural-type sarcophytol T [(*S*)-**2**] (85% yield) and unnatural-type sarcophytol A [(*R*)-**1**] (98% yield), respectively, with similar specificity as described above.

Thus, enantioselective syntheses of both enantiomers of sarcophytols A and T have been achieved using the diol **9** as a common intermediate. The [2,3]Wittig rearrangements of **12** and **13** observed in the present synthesis were unexpectedly stereospecific, although the starting bis-allyl ethers are highly flexible and the rearrangement might occur from either anions, **C** (*anti*) or **D** (*syn*), in each case. The observed results revealed that the rearrangement of (+)-**12** occurred from the anion of type **C** and that of (-)-**13** from



C (anti) **D** (syn)

the anion of type **D**, almost exclusively. Since it was very difficult to interpret the observed stereospecificity by simple analysis of molecular models, force field modeling of the transition state of the [2,3]Wittig rearrangement of **12** and **13** was carried out.[8] The lowest energy transition structures leading to (*S*)- (**12a**, **13b**) or (*R*)-alcohols (**12b**, **13a**) are shown below. The large energy difference (5.4 kcal/mol) between **13a** and **13b** rationalized the selective formation of (*R*)-**2** from (-)-**13**. In the case of (1*Z*,3*E*)-isomer **12**, **12a** is more stable than **12b** by 1.2 kcal/mol again coinciding with the observed result.



13a 13b 12a 12b

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