with allyl bromide to give cyclohexenylamine **13a**. Cyclization of **13a** with zirconocene proceeded smoothly to give the zirconacycle, which was treated with carbon monoxide at room temperature to provide the desired tricyclic ketone **12a** in 47% yield.[10] The substituent on the double bond of **13a** did not affect the zirconium-promoted reductive cyclization. Next, we attempted to isomerize the double bond of **12a** into the six-membered ring using an organometallic complex such as $RhCl_3$, $RhCl(PPh_3)_3$, or 10% Pd–charcoal, but we were unsuccessful. We overcame this problem by converting the ketone of **12a** into a methylene with $NaBH_4$ and treating the resultant product first with PhOCSCl and then with Bu_3SnH in the presence of AIBN to give compound **16** in 61% yield (3 steps). Heating **16** in the presence of TsOH in dichloroethane smoothly isomerized the double bond and afforded isomers **17**, **18**, and **19** in 46%, 25%, and 12% yields, respectively. The thermodynamically most stable isomer was **17**. Because the isomers were in a state of equilibrium in the presence of acid, **18** and **19** could be converted into **17** by heating them with TsOH in dichloroethane. Hydroboration of **17** followed by oxidation with trimethylamine *N*-oxide provided the corresponding alcohol. The benzyl group was converted to a benzyloxycarbonyl group by hydrogenolysis with 10% Pd–charcoal and subsequent treatment with carbobenzyloxy chloride in the presence of K_2CO_3. $LiAlH_4$ reduction of the carbamate **20**, followed by Jones oxidation, afforded the desired ketone **21** as a mixture of epimers. Compound **21** was treated with LDA and PhSeBr, and subsequent MCPBA oxidation afforded **11**, Kende's intermediate.[6a] The structure of **11** was confirmed by spectroscopic data.

In conclusion, a one-pot stereoselective synthesis of perhydroindole derivatives and tricyclic ketones from easily obtainable starting materials was developed using zirconium-promoted reductive cyclization. The formal total synthesis of dendrobine was achieved from the tricyclic ketone **12a**, which was prepared from (−)-carvone by a short sequence of steps.

(9) Unfortunately, compound **15** (R = H) was not optically pure (15% ee). The determination of the enantiomeric purity of compound **15** will be reported in a future article. The study of the total synthesis of optically pure dendrobine is now in progress.

(10) Cyclization of compound **13** where R = Me was unsuccessful.

Enolate Reactions on Macrocyclic Ring Systems. Total Synthesis of (±)-Sarcophytol A†

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Summary: The stereoselective synthesis of (±)-sarcophytol A and a discussion of the stereoselectivity in the β-elimination of alkoxy group of the macrocyclic enolate based on MM2 calculations are presented.

Sarcophytol A, isolated from a soft coral, *Sarcophyton glaucum*, is a cembrane-type diterpene[1] which inhibits tumor promotion by teleocidin in two-stage carcinogenesis in mouse skin.[2] We report here an efficient synthesis of sarcophytol A (**1**) by "enone switching"[3] using the β-alkoxy-α-ethylidene macrocyclic ketone **2** (Figure 1). Macrocycles have the π-orbitals of olefins oriented in the plane of the ring to minimize transannular nonbonded repulsions.[4] Therefore, macrocyclic reactions should give different senses and degrees of diastereoselectivity from those in normal five- and six-membered rings and acyclic compounds. There are extensive studies on the stereocontrolled enolate reactions in the usual cyclic and acyclic structures.[5] However, it is quite difficult to predict the stereoselectivity of macrocyclic enolate reactions[4,6] because of their many conformational possibilities. It would be an important advance if this problem could be solved.

Molecular mechanics calculations and MM2 transition structure models[7] have proven useful for prediction (or analysis) of stereoselectivity in macrocyclic reactions.[4,8] We have achieved a stereoselective synthesis of sarcophytol A (**1**) (Scheme I) in which the crucial 14-membered dienone **7** is constructed by intramolecular alkylation[9] of the protected cyanohydrin **3**, prepared from vinyl bromide **9** and farnesyl acetate **10**. The *E,Z*-diene at C(4) and C(2) in **7** is introduced stereoselectively by 1,4-addition of lithium dimethylcuprate to enone **4** followed by β-elimination of the methoxymethoxy group.[10] As described below, MM2 calculations of the various possible conformations of the exocyclic enone **4** and its likely *Z*- and *E*-enolate intermediates **5** and **6** suggest that Michael ad-

† Dedicated to Professor Gilbert Stork on the occasion of his 70th birthday.

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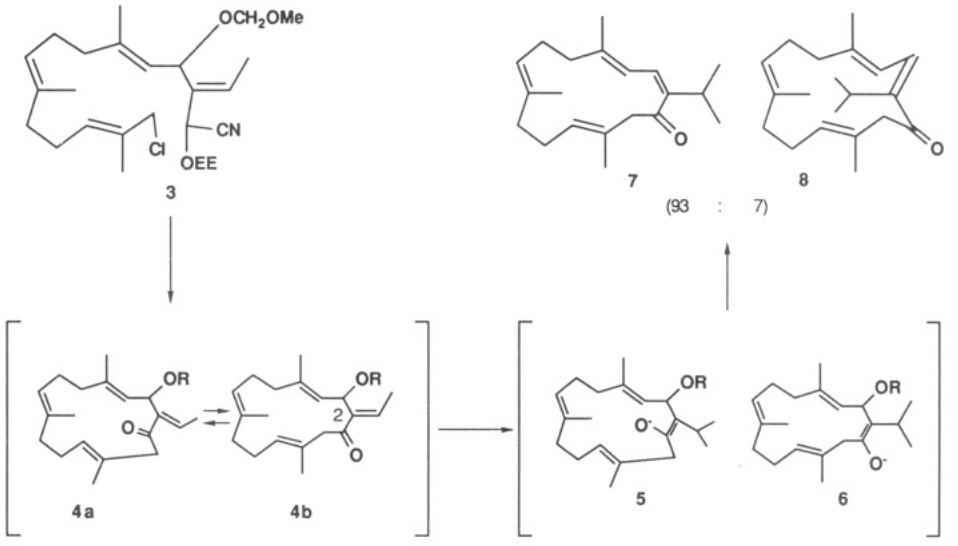
Scheme I



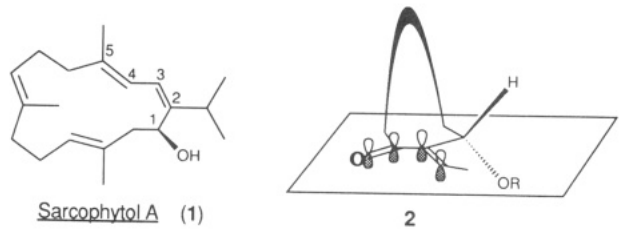
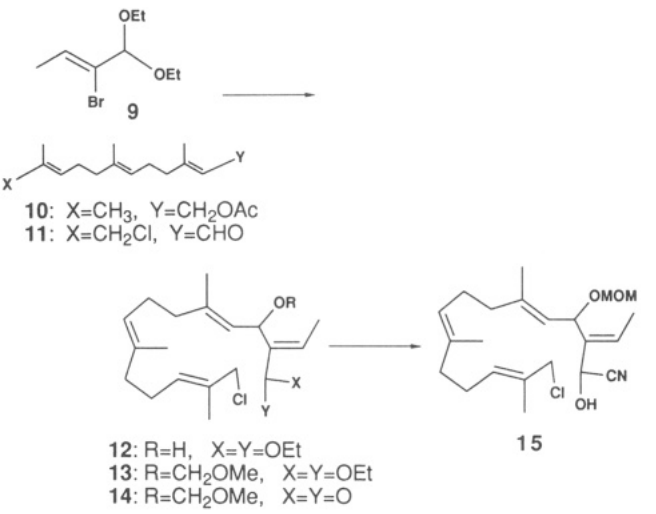


Figure 1.

Scheme II



dition to **4a** followed by β-elimination of the alkoxy group of the resulting macrocyclic *Z*-enolate **5** could provide a highly stereoselective *E,Z*-dienone **7**. Reduction of the ketone **7** with $LiAlH_4$ gives sarcophytol A (**1**).

Conformational analyses of enone **4** and its *Z,E*-enolate intermediates **5** and **6** (CH_2OMe replaced by a methyl) were conducted. At first, MULTIC[11] submode of the MACROMODEL[12] was used to search conformational space of **4**, and molecular mechanics calculations on **4** were carried out with the MM2 force field implemented in MACROMODEL. A combination of 30° torsional resolution, 1.6-Å^2 nonbonded cutoffs, 1–2-Å closure window, and 90–120° closure angles yielded 195 conformations which were submitted to the molecular mechanics calculations, and 47 optimized structures were found within 3 kcal/mol of the global minimum. Results of these calculations,[13] considering a Boltzmann distribution, showed that s-trans conformations **4a** and s-cis conformations **4b**, if equilibrated at −78 °C, would exist in a ratio 98:2. Based on the assumption of an early reactant-like transition state for the enolate formation, these calculations suggested that conjugate addition would lead to the *Z*- and *E*-enolates **5** and **6** in a ratio 98:2. Then, conformational analyses of the *Z*-enolate **5**, derived from the major s–trans **4a**, were conducted as before. MM2 calculations[13,14] of the *Z*-enolate **5** showed 27 optimized structures within 3 kcal/mol of the global minimum, which were classified into two groups, **5a** and **5b** (Figure 2), and provided the *E,Z*- and *E,E*-dienones **7** and **8**, respectively. MM2 calculations and the Boltzmann distribution of the conformers suggested that the thermodynamic equilibrium of conformations **5a** and **5b** at −78 °C would occur in a ratio 89:11. If an early reactant-like transition state for β-elimination of the alkoxy group at C(3) is assumed, it is clear that the major conformations of **5a** could yield preferential formation of the *E,Z*-dienone **7**. MM2 calculations[13] of the *E*-enolate **6**, derived from the minor *s-cis*-**4b**, showed a 97:3 ratio of **6a**:**6b**, providing *E,Z*-dienone **7** and *E,E*-dienone **8**, respectively, and also suggesting exclusive formation of *E,Z*-dienone **7**.[15]

Enone **4** was prepared in the following way (Scheme II). Lithiation of vinyl bromide **9**[16,17] (*n*-BuLi/hexane, −78 °C), followed by addition of aldehyde **11**, prepared from farnesyl acetate **10**, gave alcohol **12** in 79% yield. Protection of the secondary alcohol in **12** ($ClCH_2OCH_3$/*N,N*-diisopropylethylamine/CH_2Cl_2, 0 °C) and deprotection of the acetal **13**[17] ($CuSO_4$/MeOH–H_2O (4:1), 25 °C) gave the *E*-enal **14** in 68% overall yield from **11**. Cyanohydrin

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(17) The *Z* geometry of vinyl bromide **9** and the *E* geometry of the ethylidene group of acetal **13** are confirmed by NOE experiments.

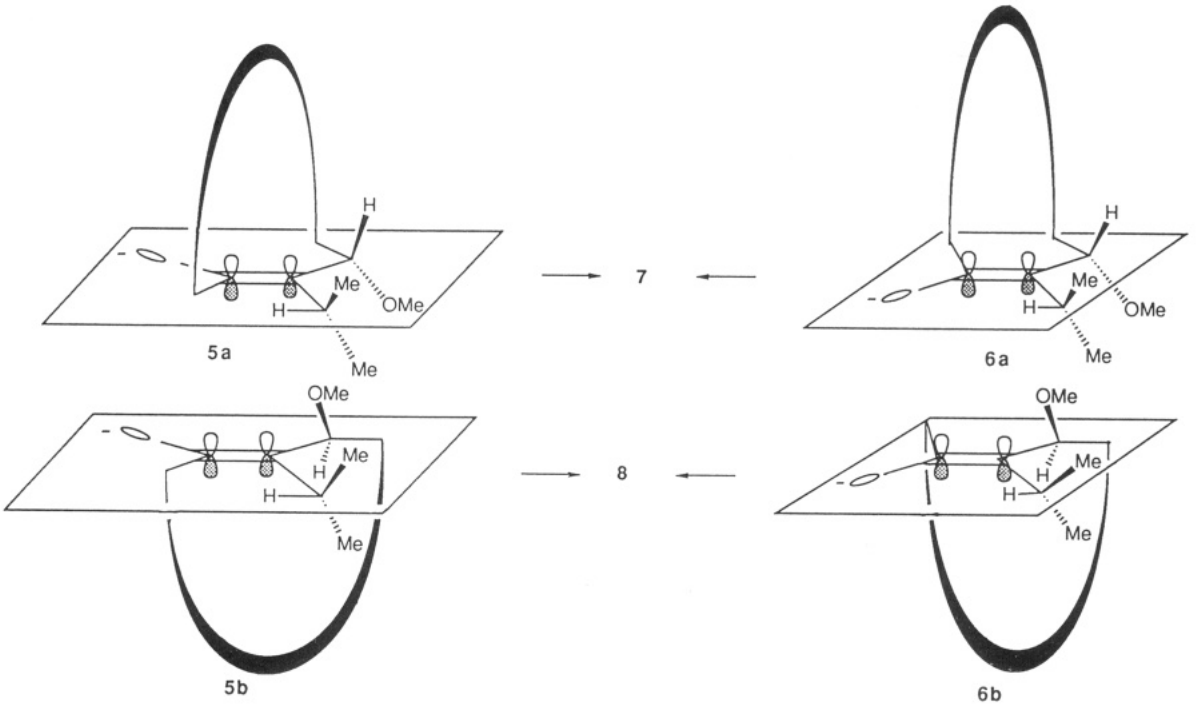

Figure 2.

formation[18] of aldehyde **14** (TMSCN/KCN/18-crown-6, 0 °C) followed by acid treatment (1 N HCl/THF, 0 °C) of the resulting cyanohydrin silyl ether gave the free cyanohydrin **15**. Reprotection of **15** with ethyl vinyl ether gave the cyanohydrin ether **3** in 56% overall yield from **14**. Cyclization of **3** (2.25 mmol) with $LiN(TMS)_2$ (21.3 mmol) in THF (50 mL) at 60 °C and acid treatment (80% aqueous AcOH–THF (1:1), 40 °C) of the cyclized product followed by basic treatment (2% aqueous NaOH, 25 °C) of the cyanohydrin gave enone **4**[19] in 69% overall yield from **3**. In these transformations, we could not detect the stereoisomers of the *E*-ethylidene group at C(2) in **4** and the regio-isomerization of the labile β',γ'-unsaturated ketone to the stable α',β'-enone.[9b]

The direct conjugate addition/β-elimination using lithium dimethylcuprate and exocyclic enone **4** in ether at −78 °C gave a mixture of endocyclic dienones **7** and **8** in 45% combined yield.[20] The HPLC analysis revealed that the "enone switching" produced a 93:7 mixture of *E,Z*- and *E,E*-dienones **7** and **8**.[21] Rationalization for this highly stereoselective β-elimination was available by MM2 calculations of the exocyclic enone **4** and the *Z*-enolate **5** as described above. The 1,4-addition of lithium dimethylcuprate to **4** in the presence of trimethylsilyl chloride and trapping of the resulting lithium enolate were unsuccessful due to a rapid β-elimination of the alkoxy group. Reduction of ketone **7** using $LiAlH_4$ at −78 °C gave (±)-sarcophytol A (**1**) in 78% yield. The ^1H NMR, ^{13}C NMR, IR, and MS spectra of the synthetic (±)-sarcophytol A (**1**) are identical with these previously reported ones.[1a] These results illustrate both the value of MM2 calculations and the importance of enolate conformational analysis for the prediction of stereoselectivity in macrocyclic reactions.

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Supplementary Material Available: Results of MM2 calculations, procedures, and spectral data (58 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(19) Enone **4**: ^1H NMR ($CDCl_3$) δ 6.75 (q, J = 7.3 Hz, 1 H), 5.66 (d, J = 9.4 Hz, 1 H), 5.41 (d, J = 9.4 Hz, 1 H), 4.82 (br s, 2 H), 4.63 (d, J = 6.6 Hz, 1 H), 4.54 (d, J = 6.6 Hz, 1 H), 3.42 (d, J = 15.1 Hz, 1 H), 3.35 (br s, 3 H), 3.02 (d, J = 15.1 Hz, 1 H), 2.00–2.30 (m, 11 H), 1.67 (s, 3 H), 1.66 (s, 3 H), 1.50 (s, 3 H). IR (neat): 2920, 1658, 1440, 1383 cm^{-1}. HRMS m/z 332.2363 (calcd for $C_{21}H_{32}O_3$ 332.2352).

(20) Dialkylated product at C(3) or C(5) was not detected, and only starting material **4** was recovered (ca. 45%).

(21) These spectra are identical with the authentic sample.[1b] *E,Z*-dienone **7**: ^1H NMR ($CDCl_3$) δ 6.21 (d, J = 11.8 Hz, 1 H), 5.88 (d, J = 11.8 Hz, 1 H). *E,E*-dienone **8**: ^1H NMR ($CDCl_3$) δ 7.22 (d, J = 11.8 Hz, 1 H), 6.44 (d, J = 11.8 Hz, 1 H).