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- (12) The electron spin resonance spectroscopic observation of the photooxidation of (Chl a-H₂O)₂ and (Chl a-2H₂O)₂ by water was reported in ref 4j, in which the biological significance of (Chl a-H₂O)₂ was also summarized. The proposal that (Chl a-2H₂O)₂ is the water splitting reaction center aggregate was suggested by this ESR observation⁴ⁱ and by the pH dependence of the photogalvanic response arising from (Chl a-2H₂O)_n-water light reactions.^{4l} The in vitro photochemical splitting of water by (Chl a-2H₂O)_n was established by the observation of gaseous evolution of H₂, HD, D₂, ¹⁶O¹⁸O, and ¹⁶O₂ by mass spectroscopy and by pyrolysis.^{4k,l} In the in vitro approach to photosynthesis research,⁴ⁱ the established properties of in vivo reaction center Chl a aggregates are compared with those of in vitro molecular adducts whose intermolecular interactions and photochemical behavior can be characterized under controlled laboratory conditions.
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Communications to the Editor

Total Synthesis of (±)-Seychellene. Use of Silyloxydienes in Synthesis¹

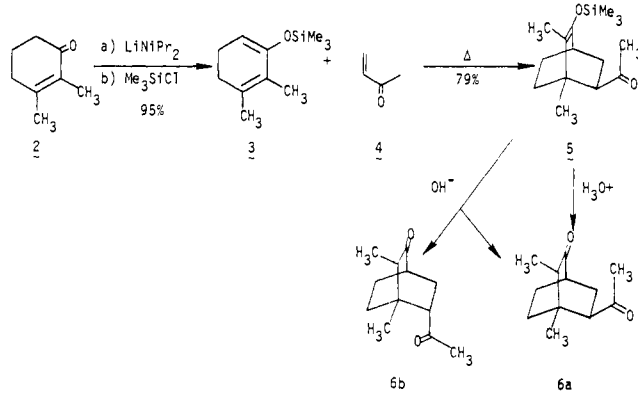
Sir:

Seychellene (**1**), a plant sesquiterpene found in commercial patchouli oil and used in perfumery,² has been a common synthetic target due to its novel tricyclic structure. Several fine syntheses of seychellene have been published³⁻⁶ which range in yield from extremely low to ≈ 7%. We wish to report now a very direct and efficient total synthesis of seychellene (**1**) in only 10 steps, which demonstrates the very high synthetic utility of 2-silyloxydienes^{7,8} in Diels-Alder approaches to polycyclic natural products.

In our approach we chose to build the necessary bicyclo[2.2.2]octane system in the first step of the synthesis with appropriate functionality so positioned that the final ring closure could be simply accomplished. To this end the 2-trimethylsilyloxyhexadiene (**3**), which was prepared in 95% yield (LDA, THF, -78 °C/Me₃SiCl) from the readily available⁹ 2,3-dimethylcyclohexenone (**2**), was reacted with methyl vinyl ketone **4** (neat, sealed tube, 110 °C, 18 h) to afford a 79% yield of the Diels-Alder adduct **5** (oil; bp 80 °C (0.2 mm); NMR (CCl₄) δ 1.90 (s, 3 H), 1.50 (s, 3 H), 1.07 (s, 3 H), 0.13 (s, 9 H); IR (liquid film) 1700, 1670 cm⁻¹) (Scheme I). We assigned the structure **5**, namely with the acetyl group endo

and 1,4 to the trimethylsilyloxy function, to this Diels-Alder product on the basis of analogy to our earlier work⁷ and to that of others⁸ which had shown that the trimethylsilyloxy group was a very good director in such cycloaddition reactions. Indirect evidence for this assignment was obtained when the silyl enol ether of **5** was hydrolyzed in acid whereupon only dione **6a** (NMR (CCl₄) δ 2.12 (s, 3 H), 1.11 (s, 3 H), 1.00 (d, 3 H), *J* = 7 Hz); IR (liquid film) 1710 cm⁻¹) was formed, and in base where a mixture of **6a** and a more stable isomer **6b** (NMR

Scheme I

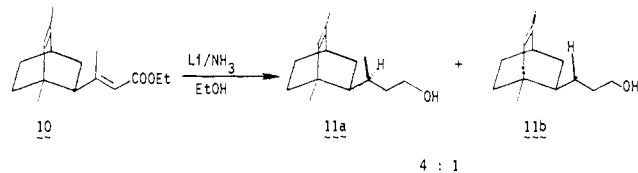
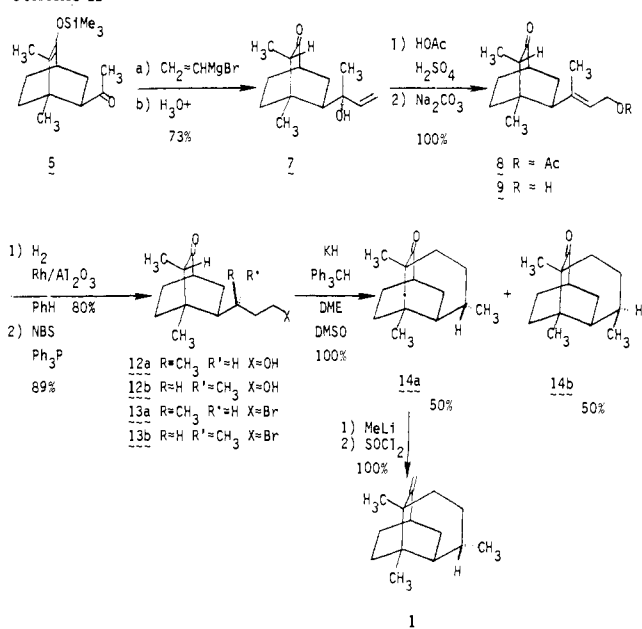


(CCl₄) δ 2.12 (s, 3 H), 0.97 (d, 3 H, $J = 6$ Hz), 0.95 (s, 3 H); IR (liquid film) 1710 cm⁻¹) was produced. Pure dione **6a** could also be converted to a mixture in which **6b** predominated by base treatment. We assumed that **6a** and **6b** are the endo (syn to carbonyl) and exo (anti to carbonyl) isomers, respectively. However, the correctness of this assignment was not proven until the completion of the synthesis when the synthetic product could be compared with authentic material.

The next step of the synthesis involved the addition of the final two carbon atoms to the side chain. This would effectively complete the sesquiterpene skeleton since the introduction of the methylene carbon of **1** from the ketone was well known.³ The use of the silyoxydiene in the initial Diels–Alder greatly facilitated this next step since it provided directly a dione monoprotected at the desired carbonyl. All attempts at two-carbon functionalization of the ketone by means of Wittig, Wadsworth–Emmons, or Reformatskii reactions failed, possibly owing to the crowded steric environment of the carbonyl of **5**. However, we were successful in adding vinylmagnesium bromide to **5** to furnish, after aqueous acid workup, the hydroxy ketone **7** (NMR (CCl₄) δ 4.9–6.4 (m, 3 H, vinyl pattern), 1.27 (s, 3 H), 1.03 (s, 3 H), 0.96 (d, 3 H, $J = 7$ Hz); IR (liquid film) 3400, 1700 cm⁻¹, 1660 cm⁻¹) as a mixture of diastereomers in 73% yield.¹⁰

Transposition of the allylic alcohol function was easily accomplished by treatment of **7** with acetic acid containing a drop of sulfuric acid to give the acetate **8**, which could be hydrolyzed in base to the alcohol **9** (NMR (CCl₄) δ 5.38 (t, 1 H, $J = 7$ Hz), 4.07 (d, 2 H, $J = 7$ Hz), 0.97 (d, 3 H, $J = 7$ Hz), 0.80 (s, 3 H); IR (liquid film) 3300, 1710, 1650 cm⁻¹), thus available from **7** in quantitative yield (Scheme II).¹⁰ By analogy to the work of Schmalzl,⁴ who reported that reduction of the acrylate **10** gave a mixture of alcohols **11a** and **11b** in which the desired

Scheme II



isomer **11a** greatly predominated, we expected that reduction of **9** should afford the desired isomer **12a** as the major isomer. In reality, a 1:1 mixture of the two alcohols **12a** and **12b** was produced upon catalytic hydrogenation over a rhodium-on-alumina catalyst. The use of other catalysts and/or solvents,¹¹ as well as attempts at dissolving metal reduction,¹² gave mainly products resulting from hydrogenolysis of the allylic alcohol function. Separation of these isomers was postponed until after the final ring closure. The alcohols **12a** and **12b** were converted with *N*-bromosuccinimide and triphenylphosphine into the bromides **13a** and **13b**, which were then cyclized to afford norseychellenone **14a** and epinorseychellenone **14b**. These isomeric ketones could be easily and quantitatively separated by column chromatography on silica gel with the desired isomer eluting first (10% EtOAc/PhH): **14a**, R_f 0.35; **14b**, R_f 0.25. The isomers were clearly distinguished by their 200-MHz NMR spectra as follows: **14a** (CCl₄), δ 1.2–2.4 (m, 13 H), 0.97 (s, 3 H), 0.94 (s, 3 H), 0.79 (d, 3 H, $J = 7$ Hz); **14b** (CCl₄), δ 1.2–2.4 (m, 13 H), 1.12 (d, 3 H, $J = 7$ Hz), 1.02 (s, 3 H), 0.98 (s, 3 H). The identity of structure **14a** was proven by comparison (NMR, IR, TLC) with an authentic sample of norseychellenone.¹³ The synthesis was completed by reaction of **14a** with methyllithium followed by dehydration with thionyl chloride according to the procedure of Piers³ to give **1** in quantitative yield, thus ending a 10-step synthesis of seychellene (**1**) from 2,3-dimethylcyclohexanone (**2**) in 20% overall yield.

The utility of this synthetic approach to highly functionalized bicyclo[2.2.2]octane derivatives, as demonstrated by this direct total synthesis of seychellene, should be quite high and is currently under investigation in our laboratory.

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- We assume that the stereochemistry of the secondary methyl group α to the ketone is anti to the alkyl residue as shown in **7**, **8**, and **9**. This anti stereochemistry would be expected to be the more stable one. Refluxing a solution of **7** with NaOMe in MeOH for 14 h does not change the 200-MHz NMR spectrum of this compound, nor is the 200-MHz NMR spectrum of **9** altered after similar treatment for 5 h.
- Several catalyst–solvent systems were employed to no avail: Pd/C–EtOAc; Pd/C, NaNO_2 –EtOAc; Pd/C, NaNO_2 –EtOH; PtO₂–EtOAc; Rh/Al₂O₃–EtOAc; Rh/Al₂O₃–EtOH.
- The α,β -unsaturated aldehyde and ester corresponding to **9** (prepared by oxidation of **7** and **9**, respectively) each afforded, upon dissolving metal reduction, a complex mixture of products which contained only minor amounts of the alcohols **12a** and **12b**.

(13) We are very grateful to Professor E. Piers for a generous sample of (\pm)-norseychellenone.

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Contribution No. 4006

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Nuclear Magnetic Resonance Manifestation of the Configurational Differences between the L- and D-Norepinephrine Complexes with Cobaltous Adenosine 5'-Triphosphate, an Aqueous Chiral Shift Reagent

Sir:

Enantiomers in achiral environments give rise to identical NMR spectra. Spectral resolution of enantiomers has been achieved by employing chiral solvents¹ or by applying chiral paramagnetic lanthanide shift reagents.² Hitherto these methods have been restricted to nonaqueous media. ATP (and its metal chelates) contains the chiral D-ribose moiety and upon association with enantiomers should provide the chiral environment necessary for spectral resolution. However, the chemical shifts induced by ATP in the protons of catecholamines are rather small, 0.3 ppm or less.³ Thus the addition of ATP to the racemic mixture of norepinephrine, $(\text{OH})_2\text{-C}_6\text{H}_3\text{C}_\beta\text{HOHC}_\alpha\text{H}_2\text{NH}_3^+$, resulted in measurable shifts for all of the protons similar to those previously obtained with the pure L enantiomer³ but no spectral resolution into enantiomers was observed. Analysis of the chemical-shift data yielded formation constants for association with ATP and intrinsic shifts in the complexed state similar to those for pure L-norepinephrine³ indicating that within the limits of resolution both enantiomers are equally complexed. This observation is in accord with the finding that complexes of catecholamines with ATP are stabilized mainly by ring stacking and by electrostatic interaction between the ammonium and phosphate groups^{3,4} and suggests that these interactions are present in the ATP complexes of both of the norepinephrine enantiomers. It is reasonable to assume, therefore, that the gross structures of the complexes are similar. In view of the structural model proposed for the ATP complexes of catecholamines,³ this similarity obviously implies different dispositions of only the substituents on the β -carbon atom relative to the ATP molecule. Schematic models of the structures of the ATP complexes with L- and D-norepinephrine are shown in Figure 1. On the basis of these models spectral resolution of enantiomers is expected for the β proton. Unfortunately this proton is not only subject to relatively small induced shifts but its resonance is obscured by the residual HDO signal of the solvent.

The chelation of a divalent metal ion by ATP results only in a slight reduction in the complexing ability of the latter for catecholamines and in minor alteration of the structure of the catecholamine-ATP complex, while offering the advantage of large dipolar shifts when Co^{2+} is the cation.⁴⁻⁶ The effect of the cobaltous ATP chelate on the aliphatic portion of the proton NMR spectrum of racemic norepinephrine is shown in Figure 2, where for comparison the spectrum of L-norepinephrine taken under similar conditions is also given. It is seen that two sets of resonances are observed with the racemic mixture: one for each enantiomer. No separation into enantiomeric signals was observed in the aromatic portion of the spectrum. At the lower temperature both the extent of association and the intrinsic shifts are enhanced resulting in higher resolution. Although the induced shift in the β proton is not the largest, it exhibits the highest dispersion as anticipated from

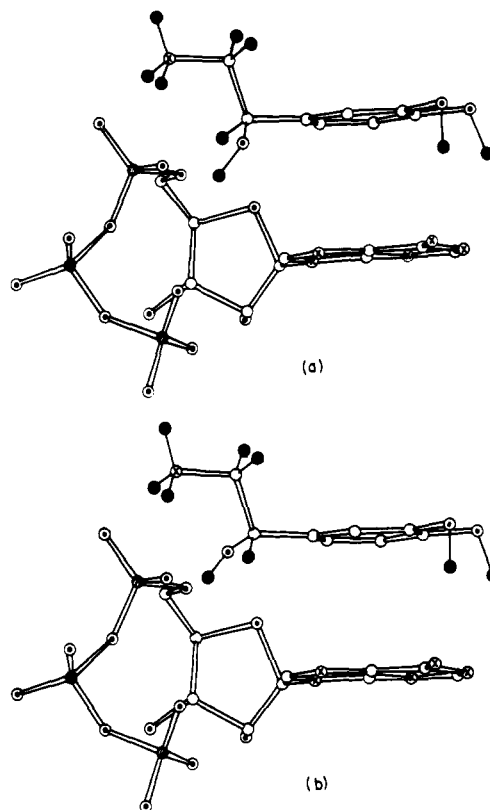


Figure 1. Schematic representation (side view) of the preferred structures of the ATP complexes with (a) L-norepinephrine and (b) D-norepinephrine.

Table I. Chemical Shifts^a Relative to the Uncomplexed State of the 1:1 Complexes of L- and D-Norepinephrine with CoATP at 27 °C

proton	L-NE	D-NE
H ₂ , ring	2.09	2.09
H ₅ , ring	2.09	2.09
H ₆ , ring	3.05	3.05
H _β	4.40	3.49
H _α	4.26	4.66
H _{α'}	5.96	5.96

^a In parts per million.

the structural models (cf. Figure 1). Since similar concentrations were employed for both samples, the facts that the protons of the L enantiomer experience the same chemical shifts when taken alone or in the racemic mixture (compare traces a and b in Figure 2) and that the aromatic protons remain unseparated indicate that the complex formation constants for the two enantiomers are the same. A formation constant of $15 \pm 3 \text{ M}^{-1}$ at 27 °C was determined from titrations of fixed norepinephrine concentrations with CoATP in a manner similar to that previously described.⁵ The chemical shifts (upfield relative to the uncomplexed state) of the norepinephrine-CoATP complexes resulting from the data analysis are summarized in Table I. The line width of the β proton in the complexed state is 21 Hz for L-norepinephrine and 13 Hz for the D enantiomer. The former value is in good agreement with the value of 19.8 Hz calculated from the longitudinal relaxation rate,⁵ indicating that the line width is governed by the dipolar interaction with the Co^{2+} ion. A distance of 4.9 Å between the β proton of L-norepinephrine and the cobaltous ion of CoATP has previously been determined from the relationship

$$1/T_1 = Cr^{-6}f(\tau_c)$$