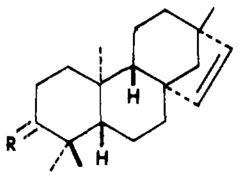
Communications

Stereoselective Total Synthesis of Racemic Stachenone[1]

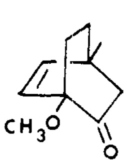
Summary: The C/D ring synthon bicyclo[3.2.1]octenedione (**4**), available from acid-catalyzed rearrangement of the bicyclo[2.2.2]octenol (**7**), was converted into the trans-fused B-C/D tricyclic derivative **5** by aldol cyclization and dissolving metal reduction and then into trans-anti-trans tetracyclic diterpene stachenone (**1**) by Robinson ring annelation and reductive alkylation in an overall yield of 16% from the starting bicyclo[2.2.2]octenone (**3**).

Sir: Stachenone (**1**), a ketonic diterpene constituent of the oleoresin of tambooti wood (*Spirostachys africana* Sond.[2]), has been assigned the tetracyclic trans-anti-trans backbone skeleton[3] characteristic of the beyerane group.[4] To date, synthetic efforts directed toward the preparation of members of this tetracyclic family have resulted in the partial[5] and total[6] synthesis of the naturally occuring enantiomeric hydrocarbons,[3] (+)-stachene (**2**) and (−)-hibaene (enantiomer of **2**). Each of these syntheses involved introduction of the D ring of the bicyclo[3.2.1]octene nucleus during the last stages of carbon skeleton construction.[7] We now wish to describe the total synthesis of stachenone (**1**), which employs the synthetic strategy of commencing with the assembly of the bicyclic C/D ring fragment and concluding with the elaboration of a fused A-B ring skeleton.[8]



1 R : O
2 R : H$_2$

Our plan can be divided into three stages: preparation of the C/D ring synthon, bicyclo[3.2.1] ketone **4**, from the bicyclo[2.2.2] ketone precursor **3**; conversion of **4** into trans-fused B-C/D tricyclic derivative **5**; and finally annelation of ring A with appropriate regio- and stereoselectivity to give stachenone (**1**).



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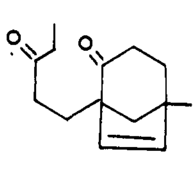

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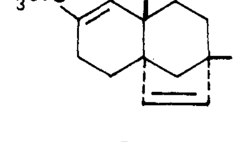

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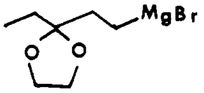
Treatment of the Diels–Alder derived 4-methyl-1-methoxybicyclo[2.2.2]oct-5-en-2-one[9] (**3**) with Grignard reagent[10] **6** (1.2 equiv; 25 °C, 20 h) furnished a mixture (2.5:1) of epimeric tertiary alcohols in 95% yield from which the major product, exo alcohol **7**, mp 56–57 °C, was isolated in 57% yield. Exposure of the exo alcohol **7** to a catalytic amount of p-toluenesulfonic acid in acetic acid (reflux, 5 h) yielded the desired bridgehead-substituted bicyclo[3.2.1]octenone **4** together with diacetate **8**. Without separation, this mixture was allowed to react with sodium methoxide in methanol (25 °C, 1 h) to give the liquid tricyclic dienone **9** [IR (CCl$_4$) 1670 cm^{-1}; NMR (CCl$_4$) δ 5.70 (d, 1, J = 6 Hz) and 5.80 (d, 1, J = 6 Hz)] in 92% overall yield from exo alcohol **7**.



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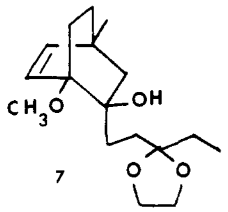

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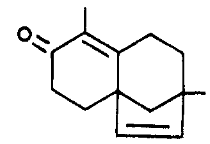

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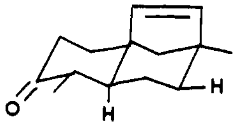
Although establishment of the required trans B-C ring fusion by dissolving metal reduction (Li/NH$_3$, ROH) of enone **9** to give ketone **10** reasonably might be expected on the basis of numerous steroid and terpene analogies,[11] the observation[12] that reduction of the structurally similar tricyclic enone **12** with lithium in liquid ammonia and ethanol yielded predominately the cis-fused product **13** (cis/trans = 10) introduced a degree of uncertainty into this transformation. In the event, reduction (Li/NH$_3$–THF, t-BuOH) of enone **9**, followed by aqueous workup, yielded a mixture (~95:5) of keto alkenes **10** and **11** as the only observed products. Assignment of the major product as the desired trans-fused derivative **10** readily followed from analysis of the vinyl region of the NMR spectrum of the mixture. The major product showed two one-proton vinyl signals at δ 5.65 and 5.90 (both d, J = 6 Hz), while the minor component showed a compressed two-proton AB system centered at δ 5.52 and 5.60. Examination of the cis-fused structure **11** reveals an apparent plane of symmetry with respect to the two vinyl hydrogen atoms and the syn substit-



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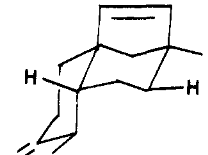

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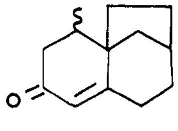

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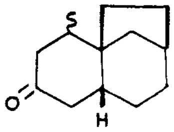

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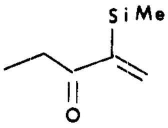
uents arrayed around the double bond. In contrast this symmetry is disrupted in the trans-fused derivative **10** due to the syn-disposed carbon atom α to the carbonyl group.[13] With this stereochemical issue now settled, the enolate anion resulting from dissolving metal reduction of **9** was trapped with trimethylsilyl chloride to give the liquid enol derivative **5** [NMR (CCl_4) δ 5.49 (d, 1, J = 5 Hz) and 5.62 (d, 1, J = 5 Hz)] in 70% yield and tricyclic ketone **10** in 20% yield.

Introduction of the A ring with the proper relative stereochemistry[14] was achieved efficiently by regioselective generation of the enolate from **5** (MeLi, DME, 25 °C), Michael addition with the α-trimethylsilyl vinyl ketone[15] **14** (−78 to 25 °C), and then aldol ring closure (NaOMe, MeOH, 3 h, Δ) to give a single tetracyclic derivative **15**, mp 59–60 °C, in 65% yield together with recovered tricyclic ketone **10** in 10% yield.



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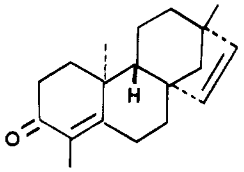

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Reductive alkylation of enone **15** (Li/NH_3, removal of NH_3 and then MeI in THF) established the necessary trans A-B ring fusion and furnished racemic stachenone **1**, mp 51–52 °C, in 67% yield together with the 2,4,4-trimethyl analogue in ~20% yield. Identity of racemic **1** [IR (CS_2) 1706, 1385, 1365, 750 cm^{-1}; NMR (CCl_4) δ 0.90 (s, 3), 1.00 (s, 6), 1.02 (s, 3), 5.48 (d, 1, J = 6 Hz), and 5.70 (d, 1, J = 6 Hz)] with natural stachenone was established by comparison of IR and NMR spectra.[16]

References and Notes

(1) Financial support of this research by the Robert A. Welch Foundation is gratefully acknowledged.
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(13) The observed downfield shift of one of the two vinyl hydrogen atoms of **10** is consistent with the steric compression resulting from the syn sp^3 α-carbon substituents: L. A. Paquette, G. Klein, and C. W. Doecke, *J. Am. Chem. Soc.*, **100**, 1595 (1978); S. Winstein, P. Carter, F. A. L. Anet, and J. R. Bourn, *ibid.*, **87**, 5247 (1965).
(14) Cf. R. K. Boeckman, Jr., *J. Am. Chem. Soc.*, **96**, 6179 (1974); G. Stork and J. Singh, *ibid.*, **96**, 6181 (1974).
(15) Cf. G. Stork and B. Ganem, *J. Am. Chem. Soc.*, **95**, 6152 (1973).
(16) Formally this work represents a synthesis of the hydrocarbons hibaene/stachene (**2**), since stachenone (**1**) has been converted into stachene (**2**).[3]

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Received December 5, 1978