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SHORT, ENANTIOSELECTIVE SYNTHESIS OF (-)-RETIGERANIC ACID VIA [2+3] ANNULATION.

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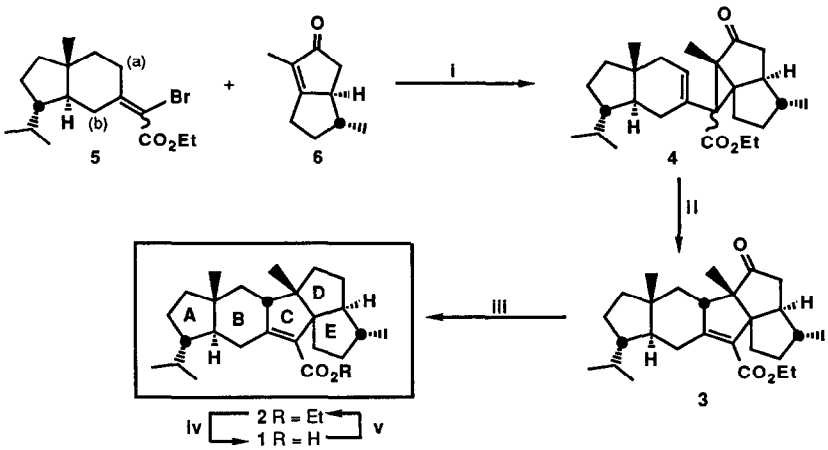
Abstract: The total synthesis of retigeranic acid **1** was achieved in 14 steps from menthene. The key features involved the vinylcyclopropanation of enone **6** with the dienolate anion of **5** to furnish vinylcyclopropane **4** and its rearrangement to pentacycle **3** in an overall [2+3] cyclopentene annulation sequence.

Retigeranic acid **1** was isolated in 1972 as the first natural product containing the tricyclo[6.3.0.$0^{2,6}$]undecane skeleton.[2] Although its appearance initiated the immense activity in the field of triquinane terpene synthesis,[3] it did not yield to total synthesis until 1985[4a] and 1987.[4b] Our initial approach to **1**, which began in 1979 and involved the [4+1] cyclopentene annulation, proved unsuccessful[5] and was abandoned in preference to a more lucrative one featuring a recently implemented vinylcyclopropanation of enones with dienolates.[6] In this paper we describe a convergent, enantioselective preparation of the title compound via [2+3] cyclopentene annulation strategy, Scheme 1.

The requisite enone **6** was prepared in four steps from keto ester **14**[7] according to the procedure of Paquette.[8] The chirality of ring-E secondary methyl group in **1** was thus incorporated by using pulegone as a starting material in direct analogy to the synthetic philosophy that led to the design and the preparation of the triquinane unit of **1** in 1981.[5]

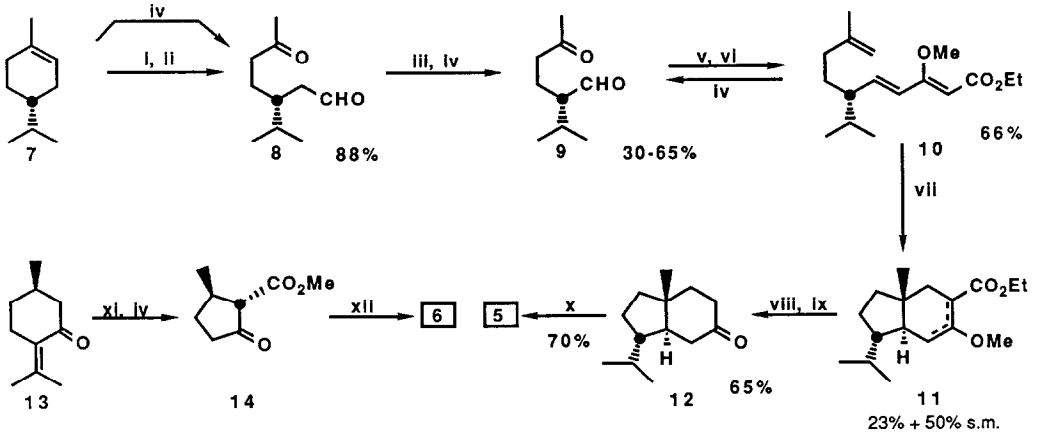


Reagents: I LDA/ THF/ -100 to -78 °C; II 585 °C/ $PbCO_3$/ 10^{-6} mm Hg; III $NaBH_4$/ MeOH; NaH/ CS_2/ MeI/ THF; n-Bu_3SnH/ AIBN/ toluene; IV KOH/ H_2O/ MeOH; V CH_3CHN_2/ Et_2O

Scheme 1

Although no data were available concerning the dienolate anion formation from substituted α-bromo crotonates such as **5**,[9a] we believed that the more accessible protons (a) would be

subject to abstraction by hindered bases.[9b] The preparation of bromo ester **5** was straightforward, albeit somewhat lengthy. We decided to use the published approaches of Fallis[10] to hydrindane **12** and to prepare this compound in an enantioselective manner. The appropriate enantiomer of **9** was prepared from menthene by ozonolysis followed by dehomologation of the aldehyde in **8** via its enamine,[11] Scheme 2. The preparation of **9** (α_D = +30.5 (c 3.03, MeOH))[12] involved chromatography after the enamine ozonolysis and proceeded in somewhat erratic



Reagents: **i** O_3/ CH_2Cl_2/ MeOH/ -78 °C; Me_2S/ p-TsOH/ RT; **ii** 3% aq. $HClO_4$/ THF/ 0 °C, 3h; RT, 3h; **iii** piperidine/ Et_2O/ 0°C; **iv** O_3/ CH_2Cl_2/ -78 °C; Me_2S; **v** ethyl 4-(dimethoxyphosphonyl)-3-methoxycrotonate/ LDA/ HMPA/ THF/ -78 to 0 °C/ 1h; **vi** $CH_3P^+Ph_3Br^-$/ n-BuLi/ THF; **vii** toluene/ 300 °C/ 8h; **viii** HCl/ THF/ RT/ 30 min; **ix** LiI/ DMF/ reflux/ 2h; **x** $TMSCHBrCO_2Et$/ LDA/ THF/ -78 °C or $TMSCH_2CO_2Et$/ LDCA/ THF/ -78 °C; Br_2/ CCl_4/ 0 °C; DBU/ DME/ 0 °C; **xi** Br_2/ pet. ether; MeONa/ MeOH; **xii** ref. 8

Scheme 2

yields (30-65%).[13] Triene **10** was prepared by sequential Wittig reactions in 66% yield from **9**. To ensure that no epimerization took place at the carbon bearing the isopropyl group, a small sample of **10** was ozonized to **9**, whose rotation was identical to that of freshly prepared material. The procedure of Fallis was followed to prepare the Diels-Alder adducts **11** (3:1 mixture of conjugated and deconjugated isomers)[10] in an isolated yield of 23% (76% based on recovered starting triene, which was recycled in further reactions). Fallis reported erratic reproducibility when dichlorobenzene was used as solvent.[10,14] With toluene and a lack of pressure-driven equilibrium during the cycloaddition, the initial cycloadduct undergoes reversible reaction and the 60:23 ratio of starting material to products most likely reflects the equilibrium composition.[15] Ketone **12** (α_D = -10.0 (c 0.07, $CDCl_3$) was obtained in 65% overall yield from **11** by hydrolysis and decarboxylation and was identical (^{1}H-NMR, TLC) with the authentic sample furnished to us by Professor Fallis.[16]

Bromo ester **5** was prepared by condensation of **12** with ethyl trimethylsilylacetate followed by introduction of α-bromide via a two-step sequence[17] or by a one-step procedure[18] involving the anion of ethyl trimethylsilyl(bromo)acetate. Treatment of **5** with LDA at -100 °C followed by addition of **6** at -78 °C gave a (1:1) mixture of exo/endo isomers of vinylcyclopropanes **4** (50%, 16% starting material). Either or both isomers were evaporated through a Vycor tube conditioned

with $PbCO_3$ to provide 75-80% yields of pentacycle **3** (α_D = +51.7 (c 0.09, $CDCl_3$)) and its isomer (4:1 from exo-**4**, 2:1 from endo-**4**).

The reduction of **3** was accomplished according to the procedure applied during the synthesis of the right-half of retigeranic acid.[5] Ketone **3** was reduced with $NaBH_4$/MeOH to a mixture of alcohols (2.5:1) and these were converted to their xanthates.[5,19] Reduction of xanthates with nBu_3SnH/AIBN in toluene[19] gave ethyl ester **2** (72% from **3**). The diagnostic protons in its ^{1}H-NMR matched those in the ^{1}H-NMR of methyl ester of **1** provided to us by Prof. Paquette [δ 2.25, q Y, 1H; δ 2.45, dd, 1H; δ 3.25, dd, 1H]. These signals also matched those of the ethyl ester of **1** derived from authentic retigeranic acid (CH_3CHN_2/Et_2O) provided to us by Prof. Shibata in 1982. The characteristic signal corresponding to the isomer of retigeranic acid, "retigeranic acid B"[4a,4b] is a doublet of doublets at 3.4 ppm. The natural product was found to be about 2:1 mixture of 1B:1A, in agreement with the findings of Corey and Shibata.[4a]

In summary, retigeranic acid was prepared in 14 steps from menthene and pulegone. Efforts are currently under way to convert the epimer of **2** to the natural configuration[20] and to study a non-thermal, TMSI-mediated rearrangement of **4** to **3**.[21] We will report the results of these endeavors in the near future.

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1. **a**, Recepient of the NIH Research Career Development Award, 1984-1989; **b**, On leave from Shanghai Academy of Science, 1986-1987; **c**, Undergraduate research participant, Longwood College, Va., Summer 1987.

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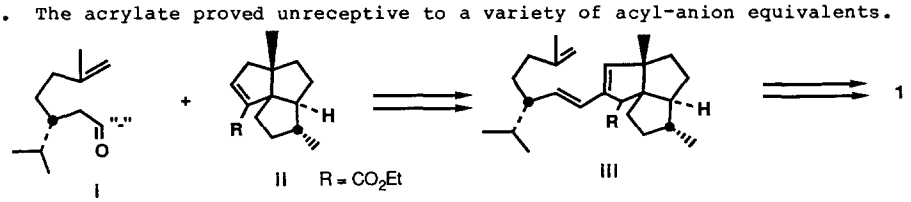
4. a, Corey, E.J.; Desai, M.C.; Engler, T.A. J. Am. Chem. Soc. **1985**, 107, 4339; **b**, Paquette, L.A.; Wright, J.; Drtina, G.J.; Roberts, R.A. J.Org. Chem. **1987**, 52, 2960.

5. The triquinane portion of **1**, namely rings C,D, and E, were synthesized in 1980 but further functionalization with the "left half" derived from menthene was not realized: Hudlicky, T.; Short, R.P. J. Org. Chem. **1982**, 47, 1522. The original thought involved the union of acrylate **i** with **ii** and elaboration to triene **iii** for the intramolecular Diels Alder approach to **1**. The acrylate proved unreceptive to a variety of acyl-anion equivalents.



I II R = CO_2Et III

6. See for example; Hudlicky, T.; Radesca, L.; Luna, H.; Anderson, F.E., III, J. Org. Chem. **1986**, 51, 4746; Hudlicky, T.; Zingde, G.S.; Natchus, M.G.; Papadopoulos, P. Tetrahedron **1987**, 43, 5685.

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8. Paquette, L.A.; Roberts, R.A.; Drtina, G.J. J. Am. Chem. Soc. **1984**, 106, 6690.

9. **a**, the dienolate formation was studied only with simple crotonates. We anticipated that the stability of the ring double bond in the dienolate of hydrindane **5** would reinforce the tendency of such dienolate to alkylate at the α-position. **b**, The removal of protons labeled (a) with hindered bases did not seem to depend on the E/Z composition of bromoesters. The E/Z composition of bromo esters was probably transferred to the exo/endo ratio of vinylcyclopropanes.

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11. White, J.D.; Ruppert, J.F.; Avery, M.A.; Torii, S.; Nokami, J. J. Am. Chem. Soc. **1981**, 103, 1813.

12. Aasen A.J.; Hlubucek, J.R.; Enzell, C.R. Acta. Chem. Scand. **1975**, B 29, 677.

13. Preparation of either methyl enol ether or TMS enol ether proved irreproducible, but the ozonolysis of enol ethers of **8** was less problematic than the ozonolysis of the enamine of **8**.

14. In our hands and "new" dichlorobenzene, trace amounts of product were obtained. Noteworthy is the observation that in "wet" dichlorobenzene the product of the Diels-Alder sequence was ketone **12**, isolated in low yield.

15. This statement is somewhat supported by the observation that "wet" solvent gave ketone **12**. Although the reaction was not clean, the ratio of starting material to this product was more favorable attesting to an equilibrium driven cycloaddition. The high-pressure alternatives to the conversion **10→11** should be investigated.

16. Prof. Fallis kindly sent us a sample of **12**, its ^{1}H-NMR, and the ^{1}H-NMR of racemic ketone prepared by Professor Corey (reference 4a).

17. Rathke, M.W.; Sullivan, D.F. Syn. Commun. **1973**, 3, 67; Taguchi, H.; Shimoji, K.; Yamamoto, H.; Nozaki, H. Bull. Chem. Soc. Jap. **1974**, 47, 2529.

18. Zapata, A.; Ferrer G., F. Syn. Commun. **1986**, 16, 1611.

19. Barton, D.H.R.; McCombie, S.W. J. Chem. Soc. Perkin Trans. I **1975**, 1574; Hart, D.J. J. Org. Chem. **1981**, 46, 367.

20. The question of equilibration of allylic ring-C methine was brought up by Prof. Paquette (ref. 4b). The assumption that the natural configuration is the more stable one is not necessary a correct one and the question needs to be addressed in detail.

21. See for example: Fleming, A.; Sinai-Zingde, G.; Natchus, M.G.; Hudlicky, T. Tetrahedron Lett. **1987**, 167.

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