The key radical cyclization–trapping sequence proved to be more sensitive to reaction conditions (particularly temperature) than expected. Heating a benzene solution (0.1 M in substrate) of the iodo acetal **6** containing 3.2 equiv of β-stannyl enone **4** and 0.1 equiv of azobisisobutyronitrile (AIBN) at 65 °C for extended periods gave no more than trace amounts of the desired adduct. Conducting the reaction at 80 °C for 10 h afforded the desired material **2c** (as a mixture of "anomers") but in only 43% isolated yield after purification by column chromatography; the same results were obtained with slow infusion (10 h) of a benzene solution of AIBN to the reaction mixture. However, simply performing the reaction at 110 °C (toluene reflux) with azobiscyclohexylnitrile as initiator[14] with 4.0 equiv of enone **4** gave **2c** in 72% isolated yield after purification by column chromatography.[15] This completes the synthesis of $PGF_{2\alpha}$ as Stork has accomplished the remaining three steps in 54% overall yield.[8]

The cyclization–trapping sequence described herein has also been accomplished with the iodo acetals **7** and **8** derived from cyclopentenol and cyclohexenol to give the expected enones **9** and **10** in 74% and 60% isolated yields, respectively (Scheme II).

In summary, the brevity, simplicity, and high level of convergence which characterize the route described herein make it a very attractive approach for the synthesis of prostaglandins and analogues and further serves to demonstrate the power of free radical carbon–carbon bond-forming reactions proceeding via addition–fragmentation pathways.[16]

(14) (a) Overberger, C. G.; Biletch, H.; Finestone, A. B.; Lilker, J.; Herbert, J. *J. Am. Chem. Soc.* **1953**, *75*, 2078 and references therein. (b) For a discussion of "some properties of radical reactions important in synthesis", note: Walling, C. *Tetrahedron Symp.* **1985**, *41*, 3887.

(15) (a) The diastereomers are readily separable at this point by chromatography over silica gel (silica gel TLC, R_f 0.17 and 0.12 in 10% ethyl acetate–hexanes). The spectral data for the individual diastereomers were identical with those available as supplementary material to ref 8. (b) The 72% yield quoted refers to material pure by HPLC analysis and C, H combustion analysis. Essentially pure material (as judged by 300-MHz NMR analysis) was isolated in considerably higher yield (98%) by simple column chromatography. Similarly, the six-ring product **10** was obtained in 99% yield via column chromatography; the yield given in the text is for material pure by HPLC analysis.

(16) Financial support of this research by the National Science Foundation is gratefully acknowledged.

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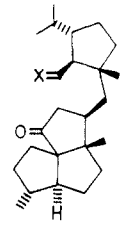
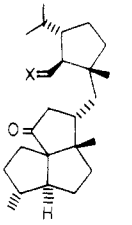
Enantiospecific Total Synthesis of Natural (−)-Retigeranic Acid A and Two (−)-Retigeranic Acid B Candidates

Summary: The total synthesis of homochiral (−)-retigeranic acid A has been achieved in a convergent manner from (*R*)-(+)-pulegone and (*S*)-(−)-limonene.

Sir: In 1972, Shibata and his associates reported the isolation[2] and structural elucidation of retigeranic acid, a unique pentacyclic triquinane sesterterpene. X-ray analysis of the highly crystalline *p*-bromoanilide served as the basis for its formulation as **1a**.[3,4] The recently completed synthesis of racemic **1a** by Corey and his associates[5] revealed native retigeranic acid to be a mixture of two isomeric substances, the minor component of which (**1a**) is now designated as retigeranic acid A.[6] These workers



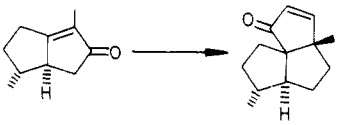
12a, X = CH_2
b, X = O



13a, X = CH_2
b, X = O

speculated the major constituent to be epimeric at the methyl-substituted center in ring E. This was subsequently shown by Shibata not to be the case.[6] In this paper, we report an enantiospecific total synthesis of (−)-**1a** by a route that was predetermined to make available as well the optically pure stereoisomers **2** and **3**, compounds considered at the outset to be realistic candidates for retigeranic acid B.

Tricyclic ketone **5** [100% ee, $[\alpha]_D^{24}$ −56.7° (*c* 0.60, $CHCl_3$)][7] of known absolute configuration was prepared from **4** as described by us previously.[8,9] The enantiomerically pure coupling partner **11** was available (Scheme I) from **6**, an aldehyde readily attainable from (*S*)-(−)-limonene.[10] The β-isopropyl configuration was utilized with notable success to install properly the absolute configuration of the quaternary carbon in **7**. Thus, application of the Still rearrangement sequence[11] to **6** gave exclusively **7**.[12] Ozonolytic cleavage of the external double bond and installation of an endocyclic olefinic center as in **8** erased the original stereocontrol element and made possible its proper reconstruction. Following oxidation to **9**, addition of vinylcuprate proceeded with predominant (77%) entry from the less hindered β-face to deliver **10**, the penultimate precursor to the desired bromide.[13]



4 **5**

(1) Continental Oil Company Fellow, 1982.

(2) Kaneda, M.; Takahashi, R.; Iitaka, Y.; Shibata, S. *Tetrahedron Lett.* **1972**, 4609.

(3) Kaneda, M.; Iitaka, Y.; Shibata, S. *Acta Crystallogr., Sect. B* **1974**, *B30*, 358.

(4) Evidently, recrystallization of the *p*-bromoanilide mixture proceeded with fractionation in favor of the less soluble *minor* constituent.

(5) Corey, E. J.; Desai, M. C.; Engler, T. A. *J. Am. Chem. Soc.* **1985**, *107*, 4339.

(6) The original suggestion for this proposed nomenclature originates from Professor Shibata, private communication, dated September 24, 1986. Disclosure of the X-ray results on retigeranic acid B was also made to us at this time.

(7) The sample of **5** utilized in the earlier work was contaminated with the regioisomeric α,β-unsaturated ketone. Its reported rotation, $[\alpha]_D^{20}$ +16.5°, is a combined consequence of its considerably lower optical purity and an unfortunate typographical error (its sign of rotation is actually levorotatory). Both samples of **5** belong to the same enantiomeric series.

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

(9) The enantiomeric purity of **5** was derived from a chiral shift reagent ^1H NMR study of **4** involving $Eu(hfc)_3$.

(10) Newhall, W. R. *J. Org. Chem.* **1958**, *23*, 1274. See also: Wolinsky, J.; Slabaugh, M. R.; Gibson, T. *Ibid.* **1964**, *29*, 3740.

(11) Still, W. C.; Mitra, A. *J. Am. Chem. Soc.* **1978**, *100*, 1927.

(12) All new compounds reported have been fully characterized by a minimum of IR, high-field ^1H NMR, and high-resolution mass spectrometry and/or combustion analysis.

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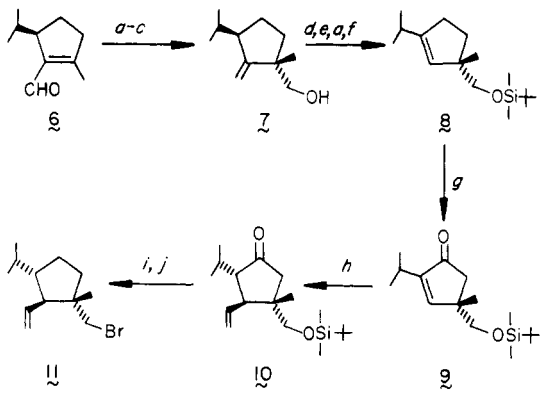
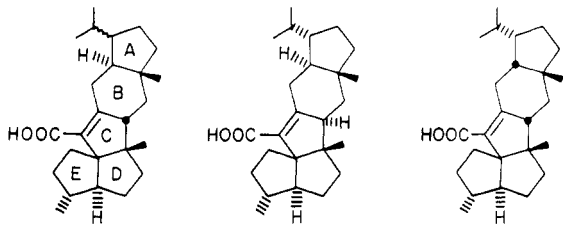
Scheme I[a]



[a] (a) Dibal-H, 100%; (b) KH, $(n\text{-Bu})_3SnCH_2I$; (c) *n*-BuLi, 75%; (d) O_3; Me_2S, 70%; (e) *i*-$PrMe_2SiCl$, imidazole, DMF, 85%; (f) $POCl_3$, py, 40–45 °C, 75%; (g) CrO_3, 3,5-dimethylpyrazole, CH_2Cl_2, 49%; (h) CH_2=$CHMgBr$, $CuBr{\cdot}SMe_2$, 50%; (i) $H_2NNH_2{\cdot}H_2O$, K_2CO_3, diethylene glycol, 190 °C, 73%; (j) Ph_3P, $ZnBr_2$, DEAD, THF, 20 °C, 91%.

The coupling of **11** to **5**, which involves C–C bond formation between two neopentyl centers, was expected to be sterically impeded. The carbonyl group in **5** is also highly congested. Admixture of the Grignard reagent from **11**[14] with **5** in ether at reflux resulted only in formation of the conjugate addition products **12a** and **13a** in a 75:25 ratio (53% isolated).[15] An electron-transfer mechanism is quite likely operative. The stereochemistry of the major isomer was confirmed by X-ray crystallographic analysis.[16]



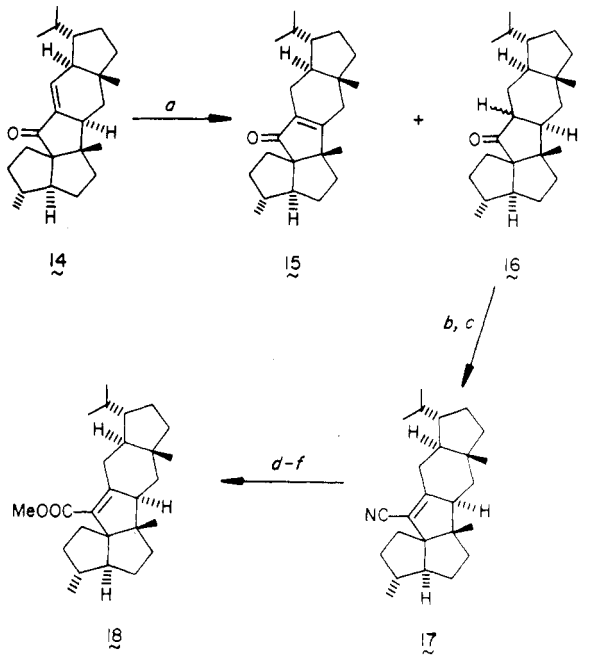
1a, α-isopropyl
b, β-isopropyl

2 **3**

Ozonolysis of **12a** gave aldehyde **12b**, whose aldol cyclization to provide **14** was best achieved (82%) through the agency of sodium hydride in refluxing toluene (Scheme II). This pentacyclic enone was next hydrogenated over platinum in acetic acid–tetrahydrofuran at 80 psi. Although the major product (**16**, 84%) was saturated, a modest amount of the unreduced isomer **15** was also formed (16%). The retention of *trans*-hydrindane stereochemistry is noteworthy (see below). Formation of the silylated cyanohydrin from **16** could only be achieved at 100 000 psi in the presence of 18-crown-6. Under these conditions, the conversion was essentially quantitative. Following the acquisition of **17**,[17] conversion to **18** proceeded smoothly. However, **18** was not identical with the methyl ester of retigeranic acid B (^1H NMR analysis).

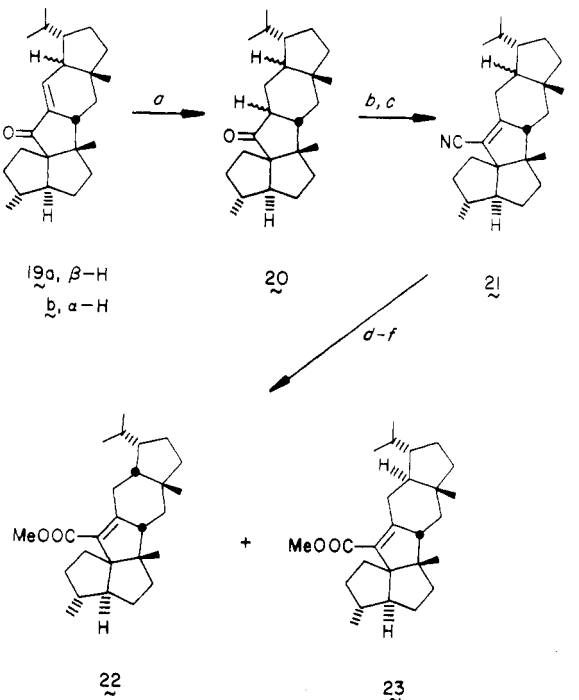
Comparable conditions were not effective at cyclizing **13**. To arrive at **19**, it was necessary to reflux the aldehyde

Scheme II[a]



[a] (a) H_2, PtO_2, THF, 80 psi, 100%; (b) Me_3SiCN, KCN, 18-crown-6, 100 000 psi, 97%; (c) $POCl_3$, DBU, py, reflux, 37%; (d) Dibal-H, −20 °C; aqueous NH_4Cl, 22%; (e) $NaClO_2$, $NaHPO_4$, *t*-BuOH, H_2O, $(CH_3)_2C$=$CHCH_3$; (f) CH_2N_2, ether.

Scheme III[a]



[a] (a) H_2, PtO_2, HOAc, THF, 80 psi, 86%; (b) Me_3SiCN, KCN, 18-crown-6, 100 000 psi, 96%; (c) $POCl_3$, DBU, py, reflux, 30%; (d) Dibal-H; Rochelle salt; H_3O^+; (e) $NaClO_2$, NaH_2PO_4, *t*-BuOH, H_2O, $(CH_3)_2C$=$CHCH_3$, 56% overall; (f) CH_2N_2, ether; HPLC, reverse phase, 92%.

with piperidine and acetic acid in toluene for 48 h. This treatment consistently delivered an 80:20 mixture of **19a** and **19b** (41%), which epimers were carried forward without separation (Scheme III). Eventually, the esters **22** and **23**, $[\alpha]_D^{23}$ −36.3° (*c* 0.155, $CHCl_3$), were isolated in a pure state by reverse-phase HPLC. The synthetic **23** was identical by infrared, ^1H NMR, and HPLC with natural (−)-methyl retigeranate A. Analysis of the 300-MHz ^1H

(13) The procedure adopted for the alcohol → bromide conversion is that of: Ho, P. T.; Davies, N. *J. Org. Chem.* **1984**, *49*, 3027.
(14) Solutions of the Grignard derivative of **11** must be used as freshly prepared. When stored at room temperature for 3 h, dimerization is complete. The very efficient process reveals the facility with which the Grignard reagent is converted to the neopentyl radical.
(15) Compare: Paquette, L. A.; Annis, G. D. *J. Am. Chem. Soc.* **1983**, *105*, 7358.
(16) The X-ray analysis was performed by Dr. J. C. Gallucci.
(17) Sugihara, Y.; Wakabayashi, S.; Saito, N.; Murata, I. *J. Am. Chem. Soc.* **1986**, *108*, 2773.

NMR spectrum of **22** conclusively indicated it to be a stereoisomer of methyl retigeranate B.

As the present investigation was nearing completion, the structure of retigeranic acid B was resolved by X-ray analysis in favor of **1b**.[6] Thus, the A and B forms differ in stereochemistry at the isopropyl-bearing carbon in ring A.

Finally, it has tacitly been assumed by several groups undertaking the de novo synthesis of **1a** that its B/C ring-fusion stereochemistry is thermodynamically the more stable. An indication that this conclusion need not necessarily be accurate stems from the dissolving metal reduction (Li, NH_3, *t*-BuOH; Swern) of **15**, which returns only **16** (83% overall). The exclusive α entry of the β hydrogen, the site normally protonated with thermodynamic control, is noteworthy.[18]

The synthesis of (−)-**1a** herein described is in principle adaptable to (−)-**1b** since the optically pure β-isopropyl equivalent of **10** is also in hand. The key features of our route—(1) the enantiospecific construction of a 1,1,2,3-tetrasubstituted cyclopentane; (2) the smooth 1,4-addition of **11** to **5** without need for copper catalysis; and (3) the high-pressure-promoted addition of Me_3SiCN to very hindered ketone carbonyls—should be achievable in this context.

(18) We are grateful to Professors S. Shibata and E. J. Corey for copies of the IR and ^1H NMR spectra of **1a,b** and their methyl esters. More recently,[6] the optical rotations of **1a,b** were made available to us by Prof. Shibata. This work was assisted financially by the National Institutes of Health (Grant GM-28468).

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Additions and Corrections

Vol. 51, 1986

Shujiro Seo,* Atsuko Uomori, and Ken'ichi Takeda. Direct Observation of the Reverse 1,5-Hydride Shift: The Mechanism of Acid-Catalyzed Isomerization at C-25 of Spirostanols.

Page 3824, column 1, line 16: C-6 and C-2 = C-2 and C-6. Table I, on the lines headed c and d: AcOD = CD_3CO_2D and CD_3CO_2D = AcOD, respectively. Footnote of Table I: 98%, and 99% = 98%, 99%, and 68%.

Page 3825, column 1, line 10: perchloric acid = perchloric [^{2}H]acid. Experimental Section, lines 9 and 11: (1) = (5).

Page 3826, column 1, line 4: **6** = **6** ($R^3 = R^4$ = 22-D = H) and **8** = **8** ($R^3 = R^4$ = 22-D = H). The end of line 49: 22 = 26. Column 2, line 43: (**10b** and **10c**) = (**10c** and **10b**).

Shuntaro Mataka, Kazufumi Takahashi, Toshizumi Hirota, Keisuke Takuma, Hiroshi Kobayashi, Masashi Tashiro,* Kiyohisa Imada, and Minoru Kuniyoshi. On the Conformation of Benzo-Annelated Bicyclo[4.4.1]undecanes, Bicyclo[5.5.1]tridecanes, and a Bicyclo[5.4.1]dodecane.

Page 4622, right column, line 2. One of the cell parameters and the cell volume for compounds **4a** were omitted. They are β = 92.70 (5)° and V = 1863 (3) Å^3, respectively.

Page 4622, right column, line 3. MoK should read Mo Kα.

Page 4622, right column, line 15. One of the cell parameters and the cell volume for compound **4d** were omitted. They are γ = 117.01 (3)° and V = 1914 (4) Å^3, respectively.

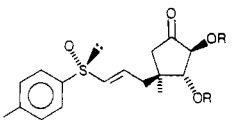
Mankil Jung,* Hala N. ElSohly, Edward M. Croom, Andrew T. McPhail, and Donald R. McPhail. Practical Conversion of Artemisinic Acid into Desoxyartemisinin.

Page 5419, column 1, line 32. The specific rotation of desoxyartemisinin (**11**) should read $[\alpha]^{19}_D$ −136.6° (*c* 0.5, CH_3OH) (lit.[7] $[\alpha]^{10}_D$ −136.4° (*c* 0.5, CH_3OH).

Vol. 52, 1987

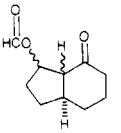
Duy H. Hua,* S. Venkataraman, M. Jo Coulter, and Gurudas Sinai-Zingde. Asymmetric Induction in the Addition Reactions of Chiral Sulfinylallyl Anions (Ambident Nucleophiles) with Enones (Ambident Electrophiles). Ring Closure of Enol Thioether Ketones.

Page 722. The structure of **8i** in Table I should be as follows:



8i

Page 724. The structure of **29f** in Table II should be as follows:



29f

Kin-ichi Tadano,* Yoko Idogaki, Hirohiko Yamada, and Tetsuo Suami*. Ortho Ester Claisen Rearrangements of Three 3-*C*-(Hydroxymethyl)methylene Derivatives of Hexofuranose: Stereoselective Introduction of a Quaternary Center on *C*-3 of D-*ribo*-, L-*lyxo*-, and D-*arabino*-Hexofuranoses.

Page 1201. Throughout this paper the assignment of stereochemistry for compounds **2**, **3**, **6**, **11**, **12**, **32**, and **33** should be reversed, i.e., **2-*E*** should be **2-*Z*** and **2-*Z*** should be **2-*E***.