(4) and the subsequent coupling with a tetrapeptide (5), followed by ring closure leading to a cyclic hexapeptide. For the first step, which is crucial to the present strategy, we employed intramolecular oxidative coupling of two phenolic parts of a L-tyrosyl-L-tyrosine derivative (6) with thallium trinitrate (TTN). Yamamura and his co-workers succeeded in preparation of derivatives of 6-bromo-2-(2,6-dibromophenoxy)phenol by TTN oxidation of 2,6-dibromophenols followed by zinc reduction.[5] In our strategy, on oxidation of an asymmetrical tetrabromo derivative (**6a**),[6] there is a possibility of the undesired **8a** being formed besides the desired **7a**. When **6a**[7] (3×10^{-3} mol/L) was treated with TTN (3 equiv) in methanol at ambient temperature, unfortunately **7a** was not detected in the reaction mixture, but **8a**[8] (33%) and **8c** (49%) were obtained. The CPK molecular model suggests that the phenolic oxygen of the left tyrosine moiety (A) of the formula **6** approaches more easily to the ortho carbon of the right tyrosine moiety (B) than the phenolic oxygen of the B ring does to the ortho carbon of the A ring. The latter approach undergoes steric retardation of the methoxycarbonyl group. To our surprise, replacement of the bromine atoms of the B ring with chlorine atoms was found to induce ring closure in the opposite fashion. Thus, treatment of dichlorodibromo derivative **6b**[9] with TTN produced the desired **7b**[10] (5.2%) and a dimethoxy dienone (**7c**, 14.4%)[11] without contamination by **8b**. Although the present reversal of the ring closure is beyond our consideration, this method appears to be generally applicable because another derivative (**6c**) of L-tyrosyl-L-tyrosine gave the corresponding **7d** (9%) and **7e** (16%) (Scheme II).

Successive treatment of **7b** with zinc in 90% acetic acid at room temperature to yield **4a** and methylation of **4a** with diazomethane in diethyl ether–methanol gave **4b**. When **4b** was subjected to catalytic hydrogenolysis on 5% Pd–C in methanol in the presence of potassium acetate, **4c**[12] was produced in an overall yield of 43% from **7b**. Condensation of **4c** with the tetrapeptide **5**[13] to afford **3a** was achieved by action of DCC in dioxane–dichloromethane. Then **3b** was obtained by saponification of **3a** with a 0.2 N solution of sodium hydroxide in methanol–acetonitrile–water (2:2:1) followed by hydrogenolysis on 5% Pd–C. On treatment of **3b** with DCC in 1,4-dioxane (about 1×10^{-2} mol/L), the final intramolecular condenstion smoothly took place to give **1a** in 39% yield. The spectral data (^{1}H NMR,[14] IR, and EI-mass), optical rotation([α]$_D$ −209° (*c* 0.03, chloroform) [lit.[3a] [α]$_D$ −229° (*c* 0.1, chloroform)]) and TLC behavior of the thus obtained **1a** were in complete agreement with those of natural RA-VII.

Further we converted **1a** to deoxybouvardin (**1b**) and RA-II (**1d**). Reaction of **1a** with aluminum trichloride in dichloromethane induced selective demethylation to afford **1b**[2] in an excellent yield.[15] On the other hand, a dihydroxy derivative (**1e**) was quantitatively given on treatment of **1a** with aluminum trichloride in the presence of a large excess of ethanethiol. Monomethylation of **1e** with diazomethane in diethyl ether–ethyl acetate (1:10) afforded **1d**[3] in 56% yield along with **1b** (6%), **1a** (14%), and the unreacted **1e** (24%). The antitumor activity of unnatural **1e** is under investigation.

Acknowledgment. We are grateful to Professor Shosuke Yamamura, Keio University, and to Dr. Noboru Mori, chief director of Ohmori Research Laboratories, Tobishi Pharmaceutical Co., Ltd. for valuable discussion.

Supplementary Material Available: Spectral and analytical data on 15 new compounds as well as synthetic deoxybouvaldin, RA-VII, and RA-II (8 pages). Ordering information is given on any current masthead page.

(5) (a) Noda, H.; Niwa, M.; Yamamura, S. *Tetrahedron Lett.* **1981**, *22*, 3247. (b) Nishiyama, S.; Yamamura, S. *Ibid.* **1982**, *23*, 1281. (c) Nishiyama, S.; Suzuki, T.; Yamamura, S. *Ibid.* **1982**, *23*, 3699. (d) Nishiyama, S.; Suzuki, T.; Yamamura, S. *Chem. Lett.* **1982**, 1851.

(6) At the final stage of our investigation, Yamamura et al. reported the application of this method to intramolecular oxidative coupling of symmetrical 3,6-bis(3,5-dibromo-4-hydroxybenzyl)-2,5-piperazinedione, which took no notice of regioselectivity: Nishiyama, S.; Nakamura, K.; Suzuki, Y.; Yamamura, S. *Tetrahedron Lett.* **1986**, *27*, 4481.

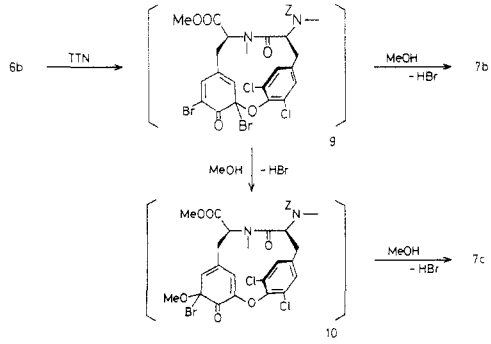
(7) **6a** was prepared in 58% yield from *N*-benzyloxycarbonyl-2,6-dibromo-*N*-methyltyrosine and 2,6-dibromo-*N*-methyltyrosine methyl ester by using DCC in 1,4-dioxane.

(8) (a) From its ^{1}H NMR ($CDCl_3$), **8a** was shown to consist of two conformers in the ratio of 4:1, which are in equilibrium at room temperature. (b) In a similar manner to the transformation of **7a** into RA-VII (**1a**) (vide infra), **8a** was derived to the corresponding bicyclic hexapeptide, the physical properties of which were not identical with those of RA-VII.

(9) **6b** was prepared in 76% yield from *N*-benzyloxycarbonyl-2,6-dichloro-*N*-methyltyrosine and 2,6-dibromo-*N*-methyltyrosine methyl ester by using DCC in 1,4-dioxane.

(10) The structure of **7b** was deduced from its IR, exact mass, and ^{1}H NMR spectra.

(11) **7b** and **7c** might be formed via a putative intermediate (**9**): Nucleophilic attack of methanol at the γ-position of **9** produces **7b**. When methanol attacks on the α-position, **7c** is formed through **10**.



(12) **4c** was shown by its ^{1}H NMR ($CDCl_3$) to consist of two conformers (5:4), which are in equilibrium at room temperature.

(13) **5** was prepared in 79% overall yield from *N*-benzyloxycarbonyl-*N*-methyltyrosine through eight steps.

(14) From its ^{1}H NMR, **1a** was shown to consist of two conformers (85:15), which were also observed in the ^{1}H NMR spectrum of natural **1a** (see ref 1b).

(15) A suspension involving **1a** and aluminum trichloride (38 equiv) in dichloromethane was stirred at room temperature for 14 h; **1b** was produced in 60% yield together with **1a** (40%).

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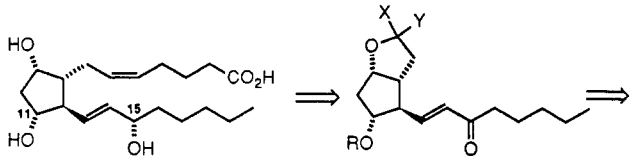
β-Stannyl Enones as Radical Traps: A Very Direct Route to $PGF_{2\alpha}$

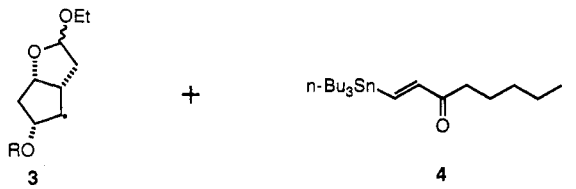
Summary: The reaction of β-stannyl enone **4** with carbon-centered radicals has been investigated. Reaction of iodo acetals **7** and **8** with **4**, under appropriate initiation conditions, afforded enones **9** and **10** via a cyclization–trapping sequence. A formal total synthesis of $PGF_{2\alpha}$ was accomplished starting from iodo acetal **6**.

0022-3263/87/1952-2958$01.50/0

Sir: Free radical or "one-electron" reactions are currently emerging as valuable tools for the construction of carbon–carbon bonds in complex systems.[1] Our own efforts in this area have focused primarily upon bimolecular processes that proceed under nonreducing conditions.[2] Chain processes involving addition of carbon-centered radicals to π systems followed by β-scission of an appropriate radical have proven highly successful for the introduction of a variety of allyl groups,[3] as well as allenyl groups,[4] α,β-unsaturated esters,[5] and styryl groups.[6] We record herein the use of such one-electron addition–fragmentation reactions in a concise synthesis of $PGF_{2\alpha}$. The route relies heavily upon previous work by Stork and coworkers, who have developed the halo acetal variant of hexenyl radical cyclization as a synthetically important reaction.[7] While our work was in progress, a report from the Stork laboratories appeared which described two routes to $PGF_{2\alpha}$ using *tert*-butyl isocyanide and α-(trimethylsilyl)octenone as traps for the radicals **3** produced in such cyclization processes.[8] We record herein the use of β-stannyl enones in such reactions.

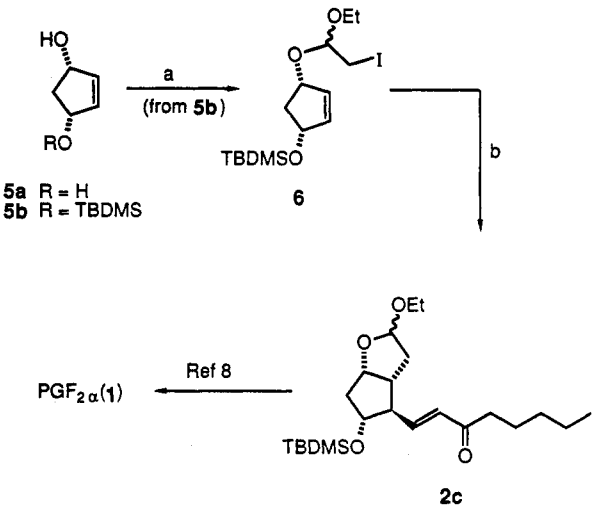


2a X,Y = O
2b X = H, Y = OH
2c X = H, Y = OEt



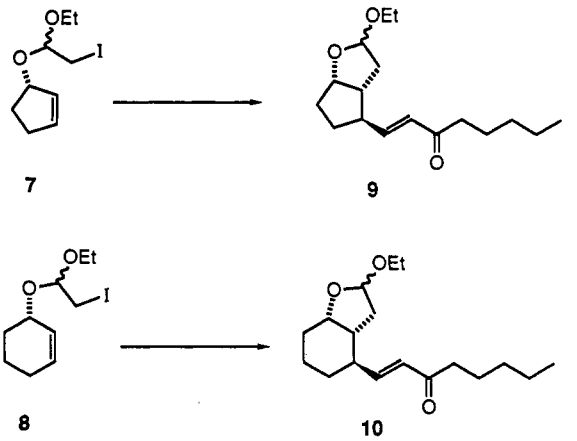
Antithetically, it is well known that reduction of the enone functionality in materials such as **2** can be controlled so as to give the desired *S* configuration at C_{15}[9] and also that the upper side chain may be installed simply by a Wittig reaction on a lactol such as **2b**.[10] The key feature of the present approach is the expectation that the entire C_{13}–C_{20} side chain could be installed with very high stereoselectivity by reaction of the radical **3** with the β-stannyl enone **4**.

Scheme I[a]



[a] (a) NIS, CH_2=CHOEt, CH_2Cl_2; (b) **4**, ACN, 110 °C, toluene.

Scheme II



Our synthesis, outlined in Scheme I, began with the known[11] diol **5a** (readily available by reaction of singlet oxygen with cyclopentadiene in the presence of thiourea), which was converted[12] to the silyl ether **5b** in 45% isolated yield. Treatment of this material with ethyl vinyl ether and *N*-iodosuccinimide in methylene chloride then afforded the iodo acetal **6** (as a mixture of diastereomers) in 91% isolated yield.[7a]

The requisite β-stannyl enone **4** was easily prepared from *trans*-1,2-bis(tri-*n*-butylstannyl)ethylene[13] in two operations (80% overall) via (1) treatment with 1.0 equiv of *n*-butyllithium (THF, −78 °C), (2) addition of 0.83 equiv of hexanal, and (3) oxidation of the resulting alcohol with pyridinium dichromate in CH_2Cl_2 at 23 °C (89%).

(1) (a) Hart, D. J. *Science (Washington, D.C.)* **1984**, *234*, 883. (b) Giese, B. *Radicals in Organic Synthesis: Formation of Carbon–Carbon Bonds*; Pergamon: New York, 1986. (c) A recent Symposium-in-Print has been devoted to radical reactions and contains many relevant articles: Giese, B., Ed. *Tetrahedron Symp.* **1985**, *41*, 3887.

(2) By "nonreducing" we mean that C–C bond formation is culminated by an event other than hydrogen abstraction.

(3) (a) Keck, G. E.; Yates, J. B. *J. Am. Chem. Soc.* **1982**, *104*, 5829. (b) Keck, G. E.; Enholm, E. J.; Yates, J. B.; Wiley, M. R. *Tetrahedron Symp.* **1985**, *41*, 4079. (c) Keck, G. E.; Byers, J. H. *J. Org. Chem.* **1985**, *50*, 5442. (d) Baldwin, J. E.; Adlington, R. M.; Birch, D. J.; Crawford, J. A.; Sweeny, J. B. *J. Chem. Soc., Chem. Commun.* **1986**, 1339.

(4) Baldwin, J. E.; Adlington, R. M.; Basak, A. *J. Chem. Soc., Chem. Commun.* **1984**, 1284.

(5) Baldwin, J. E.; Kelly, D. R.; Ziegler, C. B. *J. Chem. Soc., Chem. Commun.* **1984**, 133.

(6) Russell, G. A.; Tashtoush, H.; Ngovinatchai, P. *J. Am. Chem. Soc.* **1984**, *106*, 4622.

(7) (a) Stork, G.; Sher, P. M. *J. Am. Chem. Soc.* **1986**, *108*, 303. (b) Stork, G.; Sher, P. M. *J. Am. Chem. Soc.* **1983**, *105*, 6765. (c) Stork, G.; Mook, R., Jr. *J. Am. Chem. Soc.* **1983**, *105*, 3720. (d) Stork, G.; Mook, R., Jr.; Biller, S. A.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **1983**, *105*, 3741. (e) Stork, G.; Kahn, M. *J. Am. Chem. Soc.* **1985**, *107*, 500. (f) Stork, G. *Selectivity—A Goal for Synthetic Efficiency*; Bartman, W., Trost, B. M., Eds.; Verlag Chemie: Basel, 1984; pp 281–299.

(8) Stork, G.; Sher, P. M.; Chen, H.-L. *J. Am. Chem. Soc.* **1986**, *108*, 6384.

(9) (a) Noyori, R.; Tomino, I.; Nichizawa, M. *J. Am. Chem. Soc.* **1979**, *101*, 5843. (b) Noyori, R.; Tomino, I.; Tanimoto, Y.; Nichizawa, M. *J. Am. Chem. Soc.* **1984**, *106*, 6709. (c) Noyori, R.; Tomino, I.; Yamada, M.; Nishizawa, M. *J. Am. Chem. Soc.* **1984**, *106*, 6717.

(10) Corey, E. J.; Weinshenker, N. M.; Schaaf, T. K.; Huber, W. *J. Am. Chem. Soc.* **1969**, *91*, 5675.

(11) (a) Kaneko, C.; Sugimoto, A.; Tanaka, S. *Synthesis* **1974**, 876. (b) All compounds described herein are derived from **5a** and are racemic, although only one enantiomer is shown for convenience. The Stork route[8] employs the (−)-monoacetate of **5a** (which is available by enzyme-catalyzed hydrolysis of the diacetate of **5a**) for conversion to natural (+)-$PGF_{2\alpha}$.

(12) Corey, E. J.; Vankateswarlu, A. *J. Am. Chem. Soc.* **1972**, *90*, 6190.

(13) Corey, E. J.; Wollenberg, R. H. *J. Org. Chem.* **1975**, *40*, 3788.

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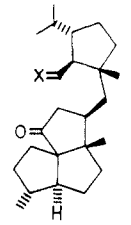
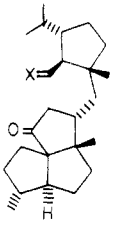
Enantiospecific Total Synthesis of Natural (−)-Retigeranic Acid A and Two (−)-Retigeranic Acid B Candidates

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



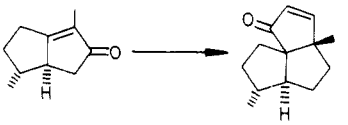
12a, X = CH_2
b, X = O



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.

0022-3263/87/1952-2960$01.50/0