hindrance to approach of the DMAD is reduced. Furthermore, it is tempting to rationalize the formation of the simple cyclization product of rearranged skeleton in eq 5, i.e., **18**, as arising from a disrotatory opening of a cyclobutene **19** which may arise by a 1,1-elimination from **13**, R″ = CH_3.[7] This speculation must await futher experimental support.

19 **18**

Acknowledgment. We thank the National Science Foundation for their generous support of our programs.

Supplementary Material Available: Typical cocyclization procedure and ^1H NMR, ^{13}C NMR, and IR data (2 pages). Ordering information is given on any current masthead page.

(7) For 1,1-eliminations from Pd^{2+}, see: Gillie, A.; Stille, J. K. *J. Am. Chem. Soc.* **1980**, *102*, 4933. Loar, M. K.; Stille, J. K. *J. Am. Chem. Soc.* **1981**, *103*, 4174. Moravskiy, A.; Stille, J. K. *J. Am. Chem. Soc.* **1981**, *103*, 4182. Numata, S.; Kurosawa, H. *J. Organomet. Chem.* **1977**, *131*, 301. For 1,1-eliminations fro Pd^{4+}, see: Ito, T.; Tsuchiya, H.; Yamamoto, A. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 1319. Kurosawa, H.; Emoto, M.; Urabe, A. *Chem. Commun.* **1984**, 968. For conversion of platinacyclobutanes to cyclopropanes, see: Hall, P. W.; Puddephatt, R. J.; Tipper, C. F. H. *J. Organomet. Chem.* **1975**, *84*, 407. Casey, C. P.; Scheck, D. M.; Shusterman, A. J. *J. Am. Chem. Soc.* **1979**, *101*, 4233.

A Chemodirected, Triply Convergent Total Synthesis of *d*-(+)-Carbacyclin[1]

D. K. Hutchinson and P. L. Fuchs*

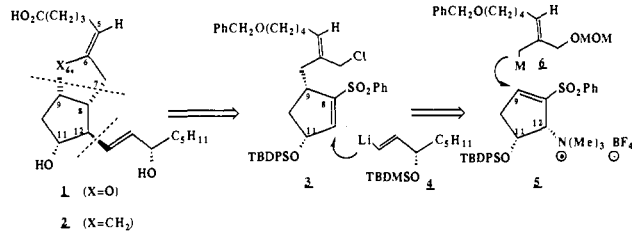
Department of Chemistry, Purdue University
West Lafayette, Indiana 47907

Received September 2, 1986

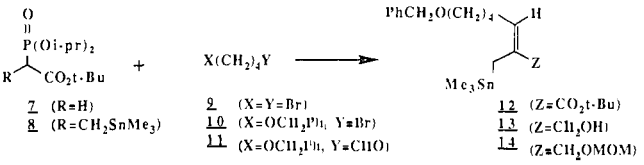
Prostaglandin I_2 (prostacyclin **1**) is well-recognized to be the prototype of a new generation of antithrombotic drugs.[2] Unfortunately, the demonstrated hydrolytic instability imparted by the enol ether moiety of **1** under physiological conditions precludes the use of this material for the inhibition of platelet aggregation.[2] A number of analogues of **1** have been prepared and among the best pharmaceutical candidates is carbacyclin (**2**).[2-4]

Previous syntheses of carbacyclin (**2**)[3] have, with two exceptions,[4] failed to stereoselectively effect either the geometry of the trisubstituted olefin or the C-15 stereocenter. Moreover, the best reported overall yield for a synthesis of chiral **2** is only ca. 0.95%.[3d]

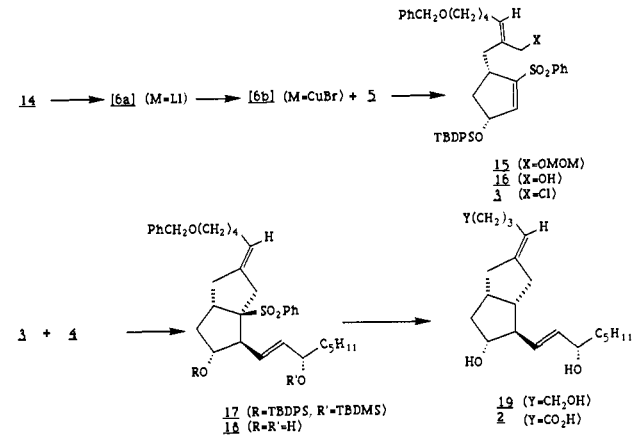
Scheme I



Scheme II



Scheme III



In conjunction with our vinyl sulfone program,[1] we wished to provide a synthesis of **2** which would remedy these difficulties. The basic plan involved a triply-convergent approach reminiscent of our earlier synthesis of 1-PGE_2[5] in that the allylic alcohol side chain was to be affixed via conjugate addition of the chiral reagent **4**[5] to vinyl sulfone **3**, a process that was expected to be highly stereocontrolled at C-12. Construction of **3** was, in turn, projected to be via S_N2' addition of the allylic organometallic reagent **6** to chiral ammonium salt **5**.[6,7] As can be readily seen from Scheme I, successful union of **5** and **6** requires control of two stereochemistries (C5,6 and C9,11) as well as two regiochemistries (C5 vs. C6a and C9 vs. C12).

Synthesis of reagent **6** was accomplished as follows: (1) Treatment of *tert*-butyl bromoacetate with triisopropyl phosphite at 90–215 °C affords a 95% yield of phosphonate ester **7**[8] which is subsequently deprotonated with sodium hydride in THF followed by reaction with trimethyliodomethylstannane[9] to provide **8**[8] in 95% yield. (2) Reaction of excess (3 equiv) 1,4-dibromobutane

(1) Syntheses via vinyl sulfones. 22. For the previous paper in this series, see: Toth, J. E.; Fuchs, P. L. *J. Org. Chem.* **1987**, *52*, 473.

(2) (a) Bartmann, W.; Beck, G. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 751–764. (b) Newton, R. F.; Roberts, S. M.; Taylor, R. J. K. *Synthesis* **1984**, 449–478.

(3) (a) Konishi, Y.; Kawamura, M.; Iguchi, Y.; Arai, Y.; Hayashi, M. *Tetrahedron* **1981**, *37*, 4391. (b) Skuballa, W.; Vorbruggen, H. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 1046. (c) Aristoff, P. A. *J. Org. Chem.* **1981**, *46*, 1954. (d) Shibasaki, M.; Sodeoka, M.; Ogawa, Y. *J. Org. Chem.* **1984**, *49*, 4096. (e) Shibasaki, M.; Iseki, K.; Ikegami, S. *Chem. Lett.* **1979**, 1299. (f) Yamazaki, M.; Shibasaki, M.; Ikegami, S. *Chem. Lett.* **1981**, 1245. (g) Amemiya, S.; Kojima, K.; Sakai, K. *Chem. Pharm. Bull.* **1984**, *32*, 1349. (h) Nicolaou, K. C.; Spiro, W. J.; Magolda, R. L.; Seitz, S.; Barnette, W. E. *J. Chem. Soc., Chem. Commun.* **1978**, 1067. (i) Shibasaki, M.; Veda, J.-I.; Ikegami, S. *Tetrahedron Lett.* **1979**, *20*, 433. (j) Morton, D. R., Jr., Brokaw, F. C. *J. Org. Chem.* **1979**, *44*, 2880. (k) Sugie, A.; Shimomura, H.; Katsube, J.; Yamamoto, H. *Tetrahedron Lett.* **1979**, *20*, 2607. (l) Kojima, K.; Sakai, K. *Tetrahedron Lett.* **1978**, *19*, 3743. (m) Barco, A.; Benetti, S.; Pollini, G. P.; Baraldi, P. G.; Gandolfi, C. *J. Org. Chem.* **1980**, *45*, 4776.

(4) Control of the reduction of an enone at C-15 has been reported to afford a 94:6 ratio of the (*S*)- and (*R*)-alcohols,[3a] and the stereochemistry of the trisubstituted olefin has been shown to be stereospecifically effected by 1,4-hydrogenation of a diene.[3d] In neither of these papers were *both* of these stereochemical problems solved.

(5) (a) Donaldson, R. E.; Fuchs, P. L. *J. Am. Chem. Soc.* **1981**, *103*, 2108. (b) Donaldson, R. E.; Saddler, J. C.; McKenzie, A. T.; Byrn, S.; Fuchs, P. L. *J. Org. Chem.* **1983**, *48*, 2167.

(6) Hutchinson, D. K.; Fuchs, P. L. *J. Am. Chem. Soc.* **1985**, *107*, 6137.

(7) Chiral **5** is available in 19.9% overall yield from cyclopentadiene via an enantioconvergent process (see: ref 6 and Donaldson, R. E.; Saddler, J. C.; Fuchs, P. L. *J. Am. Chem. Soc.* **1981**, *103*, 2110.).

(8) This compound exhibited satisfactory spectral and analytical properties. Yields refer to material of >95% purity. $[\alpha]_D^{25}$ values are recorded in the following form (compound number; rotation; concentration; solvent): **15**: +20.8°, (*c* 0.680, CH_2Cl_2); **16**: +23.7°, (*c* 0.720, $CHCl_3$); **3**: +5.5°, (*c* 0.780, $CHCl_3$); **17**: +4.4°, (*c* 0.770, $CHCl_3$); **18**: +62.4°, (*c* 1.610, $CHCl_3$); **19**: +72.4°, (*c* 1.230, $CHCl_3$).

(9) Trimethyliodomethylstannane was prepared by a modification of the method of Seyferth (Seyferth, D.; Andrews, S. B. *J. Organomet. Chem.* **1971**, *30*, 151.). We find this to be an economically preferable solution to the more recent preparation proposed by Seitz (Seitz, D. E.; Carroll, J. J.; Cartaya, M. C. P.; Lee, S.-H.; Zapata, A. *Synth. Commun.* **1983**, *13*, 129.).

0002-7863/87/1509-4755$01.50/0

(9) with benzyl alcohol under phase-transfer conditions (C_6H_6, NaOH, n-Bu_4NHSO_4 (5%), 25 °C, 40 h) smoothly affords monobromide **10**[8] in 80% yield. Conversion of **10** to the Grignard reagent (Mg, THF, 4 h 35 °C), followed by addition of triethyl orthoformate (2 equiv, 18 h, reflux) and hydrolytic workup (5% HCl/THF), provides aldehyde **11**[8] in 66% yield. (3) Treatment of phosphonate **8** in THF with sodium hydride (catalytic H_2O required[10]) followed by addition of aldehyde **11** (4 h, 25 °C) and extractive workup results in the highly selective[11] generation of vinyl ester **12**[8] (87%). Reduction of the ester moiety of **12** (DIBAL, CH_2Cl_2, 25 °C, 24 h) afforded alcohol **13**[8] (89%) which was protected[12] to afford acetal **14**[8] in 91% yield (Scheme II).

Conversion of allylstannane **14** to the requisite "trimethylenemethane[13,14a]" reagent was accomplished by treatment with n-butyllithium in THF at −78 °C to produce allyllithium species **6a**[15] which was treated with freshly prepared copper(I) bromide–dimethyl sulfide complex[16] in the presence of lithium bromide (3 equiv) providing bromocuprate **6b**.[17] Reaction of **6b** (1.1 equiv) with optically active **5**[6,7] (THF, −55 °C, 30 min) affords **15**[8] (Scheme III) (74%) as a single stereoisomer as assayed by HPLC and NMR.[18] Deprotection of **15** with 3 equiv of dimethylboron bromide[19] in dichloromethane at −78 °C for 1 h provides alcohol **16**[8] in 85% yield. Conversion of **16** to allyl chloride **3**[8] (98% yield) was smoothly accomplished by using the Corey–Kim protocol.[20] Reaction of **3** with the chiral vinyllithium reagent **4**[5] (THF, −78 °C, 15 min; −50 °C, 10 min) affords the bicyclic sulfone **17**[8,14] (95% yield) which is subsequently desilylated by treatment with 10 equiv of tetrabutylammonium fluoride[21] in THF for 24 h at 25 °C providing diol **18**[8] in 80% yield. Treatment of **18** with 20 equiv of lithium in liquid ammonia containing 4 equiv of *tert*-butyl alcohol (THF cosolvent, −78 °C, isoprene quench after 15 min) affords the desulfonylated, debenzylated triol **19**[8] in 88% yield. Completion of the synthesis was conveniently achieved by a method first utilized by Fried for oxidation of a PGF triol.[22] Oxidation of triol **19** with Pt/O_2 in 1:10 acetone–water containing 19 equiv of sodium bicarbonate at 57 °C for 2 h afforded a 57% yield of **2**.[23] Comparison of the synthetic material with an authentic sample of (*E*)-carbacyclin[24] reveals the stereochemistry at C5,6 to be >96% *E*, consistent with the stereochemical purity of the "trimethylenemethane" reagent.[11] Thus the overall yield from cyclopentadiene for this triply-convergent process is 4.7%, including the resolution step.

Acknowledgment. We thank the NIH (GM-32693) for partial support of this research. D.K.H. thanks Procter and Gamble for a graduate fellowship. We thank the Purdue University Biological Magnetic Resonance Laboratory (NIH-RR01077) for access to the 470-MHz ^1H NMR spectrometer. We acknowledge the NSF for an XL200 spectrometer (CHE-80-04246). Thanks are also due to Tamin Braish, Mark Anderson, John Toth, and Tim Burkholder for spectral and computational assistance and to Steve Cook and Terry Miller for assistance with reverse-phase HPLC work.

(10) (a) Pietrusiewicz, K. M.; Monkiewicz, J. *Tetrahedron Lett.* **1986**, *27*, 739. (b) Pietrusiewicz, K. M.; Monkiewicz, J.; Bodalski, R. J. *J. Org. Chem.* **1983**, *48*, 788 and references cited therein.

(11) The stereoselectivity of this process is 96:4 as assayed by HPLC. Use of the triethoxy reagent gave an 85:15 mixture of vinyl esters which were effectively inseparable by preparative chromatography.

(12) Stork, G.; Takahashi, T. *J. Am. Chem. Soc.* **1977**, *99*, 1275.

(13) The parent 2-oxygenated 3-allylstannanes have been utilized by the Trost group as trimethylenemethane precursors (*J. Am. Chem. Soc.* **1985**, *107*, 719, 1778.), and a trisubstituted reagent has recently been utilized by Schlessinger and Wood for 1,2-addition to an aldehyde by using Lewis acid catalysis (see: Schlessinger, R. H.; Wood, J. L. *J. Org. Chem.* **1986**, *51*, 2621.), but apparently **14** represents the first example of an oxygenated allylstannane bearing a stereodefined trisubstituted olefin being used for allyl anion generation.

(14) The overall synthetic strategy is formally equivalent to a regiospecific, stepwise trimethylenemethane 3 + 2 cycloaddition to a vinyl sulfone. For examples of trimethylenemethane 3 + 2 cycloadditions with vinyl sulfones, see: (a) Little, R. D.; Brown, L. *Tetrahedron Lett.* **1980**, *21*, 2203. (b) Trost, B. M.; Chan, D. M. T. *J. Am. Chem. Soc.* **1982**, *104*, 3733.

(15) Seyferth has shown that simple allylstannanes undergo transmetalation with methyllithium at 0 °C to afford allyllithium reagents (Seyferth, D.; Mammarella, R. E. *J. Organomet. Chem.* **1979**, *177*, 53.). The ability of nearby oxygen functionality to promote this exchange process, as seen with **14**, has also been reported by Carpenter (Newman-Evans, R. H.; Carpenter, B. K. *Tetrahedron Lett.* **1985**, *26*, 1141).

(16) (a) House, H. O.; Chu, C.-Y.; Wilkins, J. M.; Umen, M. J. *J. Org. Chem.* **1975**, *40*, 1460. (b) Theis, A. B.; Townsend, C. A. *Synth. Commun.* **1981**, *11*, 157.

(17) Hutchinson, D. K.; Hardinger, S. A.; Fuchs, P. L. *Tetrahedron Lett.* **1986**, *27*, 1425.

(18) A survey of the reaction of **5** with a series of allylic organometallic reagents (α/γ ratios; C-9/C-11 stereocontrol; trisubstituted olefin stereointegrity) will be described in detail subsequently in a full paper.

(19) Guindon, Y.; Yoakim, C.; Morton, H. E. *J. Org. Chem.* **1984**, *49*, 3912.

(20) Corey, E. J.; Kim, C. U.; Tadeka, M. *Tetrahedron Lett.* **1972**, *13*, 4339.

(21) (a) Corey, E. J.; Venkatswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190. (b) Hanessian, S.; Lavallee, P. *Can. J. Chem.* **1975**, *53*, 2975.

(22) Fried, J.; Sih, J. C. *Tetrahedron Lett.* **1973**, *14*, 3899. In contrast to Fried's substrate, we were able to use a 1:1 PtO_2/substrate ratio.

(23) Although the "crude" carbacyclin obtained as an oil from this reaction was found to be >96% pure, with an *E*:*Z* = >99:1 by HPLC [25 cm × 4.6 mm Hi-chrom reversible HPLC column ODS-II (Regis Chemical Co.), mobile phase 45/55 (acetonitrile/0.01 M KH_2PO_4 adjusted to pH 2.5 with concentrated H_2SO_4), flow rate 1 mL/min, detection at 205 nm], and provided an essentially superimposable 470-MHz ^1H NMR spectra with that of an authentic sample;[24] it could not be made to crystallize, even by addition of a seed crystal. An analytical sample was prepared by treatment of the carbacyclin with diazomethane and then with acetic anhydride and triethylamine in the presence of catalytic 4-(dimethylamino)pyridine. The methyl ester diacetate was purified by medium pressure liquid chromatography by using a Merck size C lobar column. The purified material was saponified and chromatographed over Mallincrodt CC-4 special acid washed silica gel, followed by recrystallization from ether–hexane. The crystalline carbacyclin thus obtained in 34% yield (1.6% overall from cyclopentadiene) had an identical HPLC profile with that of the oily material under the aforementioned conditions. The carbacyclin obtained had the following physical data: mp 60–62.3 °C (lit. mp 62.4–63.3 °C,[3j] 64.5–66.5 °C,[3a] 61–62.5 °C[3c]), $[\alpha]_D^{25}$ +95.2° (*c* 0.520, MeOH) (lit. $[\alpha]_D^{25}$ + 90° (*c* 0.810, MeOH),[3i] $[\alpha]_D^{25}$ + 92.2° (*c* 0.515, MeOH),[3a] $[\alpha]_D^{25}$ + 91° (*c* 0.964, MeOH)[3c]).

(24) We thank Dr. John Pike of the Upjohn Company for an authentic sample of (*E*)-carbacyclin (**2**).

Dramatic Rate Enhancement of Suzuki Diene Synthesis: Its Application to Palytoxin Synthesis

Jun-ichi Uenishi, Jean-Marie Beau, Robert W. Armstrong, and Yoshito Kishi*

Department of Chemistry, Harvard University Cambridge, Massachusetts 02138

Received March 2, 1987

In connection with the synthetic studies on the marine natural product palytoxin,[1] we have investigated the possibility to form the C.75–C.76 bond[2] by using the Pd(0)-mediated diene synthesis developed by Suzuki and co-workers.[3] More specifically, we were interested in utilizing this reaction to couple the upper and lower halves in order to assemble the complete carbon backbone of palytoxin. We chose the model system of **1**[4] + **2** → **3** to clarify

(1) For the synthetic studies on palytoxin, see: Jin, H.; Uenishi, J.; Christ, W. J.; Kishi, Y. *J. Am. Chem. Soc.* **1986**, *108*, 5644 and references cited therein.

(2) For the complete structure and numbering of palytoxin, see: Cha, J. K.; Christ, W. J.; Finan, J. M.; Fujioka, H.; Kishi, Y.; Klein, L. L.; Ko, S. S.; Leder, J.; McWhorter, W. W., Jr.; Pfaff, K.-P.; Yonaga, M.; Uemura, D.; Hirata, Y. *J. Am. Chem. Soc.* **1982**, *104*, 7369.

(3) (a) Miyaura, N.; Yamada, Y.; Suzuki, A. *Tetrahedron Lett.* **1979**, *20*, 3437. (b) Miyaura, N.; Suginome, H.; Suzuki, A. *Tetrahedron Lett.* **1981**, *22*, 127. (c) Miyaura, N.; Yamada, K.; Suginome, H.; Suzuki, A. *J. Am. Chem. Soc.* **1985**, *107*, 972.

0002-7863/87/1509-4756$01.50/0