J|A|C|S
ARTICLES
Published on Web 02/16/2002

Total Synthesis of the CP-Molecules (CP-263,114 and CP-225,917, Phomoidrides B and A). 1. Racemic and Asymmetric Synthesis of Bicyclo[4.3.1] Key Building Blocks

K. C. Nicolaou,* J. Jung, W. H. Yoon, K. C. Fong, H.-S. Choi, Y. He, Y.-L. Zhong, and P. S. Baran

Contribution from the Department of Chemistry and The Skaggs Institute for Chemical Biology, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037, and Department of Chemistry and Biochemistry, University of California, San Diego, 9500 Gilman Drive, La Jolla, California 92093

Received August 20, 2001

Abstract: A brief introduction into the chemistry of the CP-molecules is followed by first-generation synthetic sequences toward key building blocks for their total synthesis. Processes for both racemic and enantiomerically enriched bicyclo[4.3.1] ketone **6** or its equivalent are described, and the absolute stereochemistries of the optically enriched intermediates are determined. The efficient route developed to racemic **6** and the ready access to both enantiomers of key building blocks provided the opportunity for the total synthesis of the CP-molecules and determination of their absolute stereochemistry.

Introduction

Since their discovery in the mid-1990s by a group at Pfizer,[1] the CP-molecules [**1**, CP-263,114 (phomoidride B), and **2**, CP-225,917 (phomoidride A), Figure 1] have stimulated manifold studies directed toward their total synthesis.[2] The intense interest[3] in these natural products is fueled by their interesting biological activities[1] (inhibitors of ras farnesyl transferase and squalene synthase) and complex and unusual molecular connectivities. Indeed, the exquisite chemical architectures of the CP-molecules and the sheer challenge associated with their total synthesis demand and inspire the design, development, and discovery of new synthetic methods and novel synthetic strategies.[4]

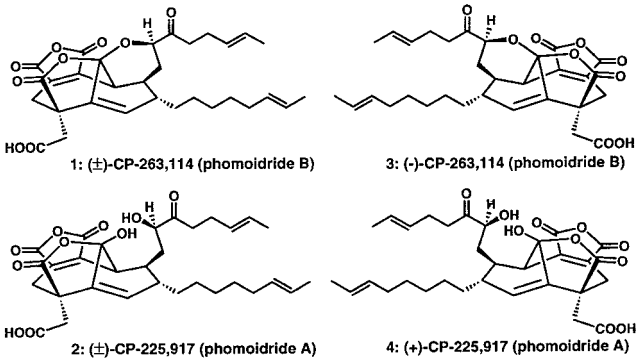


Figure 1. Structures and absolute configurations of the CP-molecules. For the purposes of this series of papers, structures **1** and **2** will designate the racemic compounds, whereas structures **3** and **4** will designate the proven naturally occurring enantiomeric forms of the CP-molecules.

In 1999 we reported the first total syntheses of **1** and **2** (racemic),[5] and in 2000 we determined their absolute configurations (**3** and **4**, as shown in Figure 1) by way of asymmetric

* To whom correspondence should be addressed at the Department of Chemistry, The Scripps Research Institute.

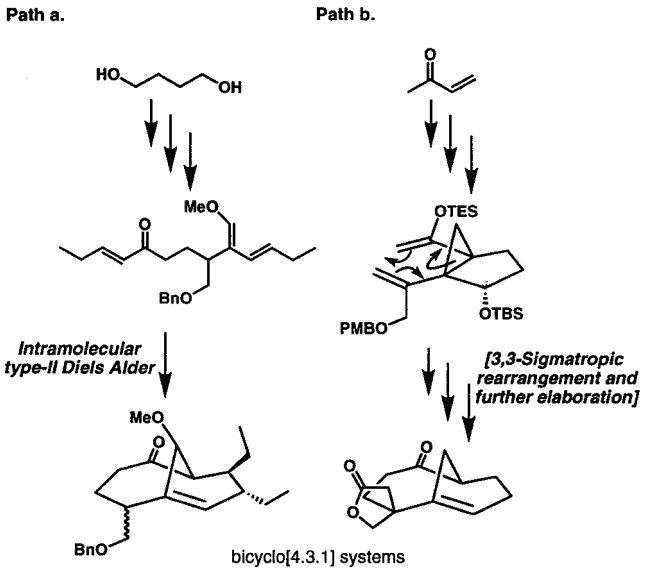
(1) (a) Dabrah, T. T.; Kaneko, T.; Massefski, Jr., W.; Whipple, E. B. *J. Am. Chem. Soc.* **1997**, *119*, 1594. (b) Dabrah, T. T.; Harwood, H. J., Jr.; Huang, L. H.; Jankovich, N. D.; Kaneko, T.; Li, J.-C.; Lindsey, S.; Moshier, P. M.; Subashi, T. A.; Therrien, M.; Watts, P. C. *J. Antibiot.* **1997**, *50*, 1. (c) For an earlier disclosure of the structures of the CP-molecules, see: Stinson, S. *Chem. Eng. News* **1995**, May 22, 29.

(2) (a) Nicolaou, K. C.; Härter, M. W.; Boulton, L.; Jandeleit, B. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1194. (b) Nicolaou, K. C.; Postema, M. H. D.; Miller, N. D.; Yang, G. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2821. (c) Davies, H. M. L.; Calvo, R.; Ahmed, G. *Tetrahedron Lett.* **1997**, *38*, 1737. (d) Sgarbi, P. W. M.; Clive, D. L. J. *Chem. Commun.* **1997**, 2157. (e) Armstrong, A.; Critchley, T. J.; Mortlook, A. A. *Synlett* **1998**, 552. (f) Kwon, O.; Su, D.-S.; Meng, D.; Deng, W.; D'Amico, D. C.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1877. (g) Kwon, O.; Su, D.-S.; Meng, D.; Deng, W.; D'Amico, D. C.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1880. (h) Waizumi, N.; Itoh, T.; Fukuyama, T. *Tetrahedron Lett.* **1998**, *39*, 6015. (i) Chen, C.; Layton, M. E.; Shair, M. D. *J. Am. Chem. Soc.* **1998**, *120*, 10784. (j) Fontier, A. J.; Danishefsky, S. J.; Koppel, G. A.; Meng, D. *Tetrahedron* **1998**, *54*, 12721. (k) Bio, M. M.; Leighton, J. L. *J. Am. Chem. Soc.* **1999**, *121*, 890. (l) Nicolaou, K. C.; Baran, P. S.; Jautelat, R.; He, Y.; Fong, K. C.; Choi, H.-S.; Yoon, W. H.; Zhong, Y.-L. *Angew. Chem., Int. Ed.* **1999**, *38*, 549. (m) Clive, D. L. J.; Sun, S.; He, X.; Zhang, J.; Gagliardini, V. *Tetrahedron Lett.* **1999**, *40*, 4605. (n) Meng, D.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **1999**, *38*, 1485. (o) Yoshimitsu, T.; Yanagiya, M.; Nagaoka, H. *Tetrahedron Lett.* **1999**, *40*, 5215. (p) Meng, D.; Tan, Q.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **1999**, *38*, 3197. (q) Sulikowski, G. A.; Agnelli, F.; Corbett, R. M. *J. Org. Chem.* **2000**, *65*, 337. (r) Devaux, J.-F.; O'Neil, S. V.; Guillo, N.; Paquette, L. A. *Collect. Czech. Chem. Commun.* **2000**, *65*, 490. (s) Davies, H. M. L.; Calvo, R. L.; Townsend, R. J.; Pingda, R.; Churchill, R. M. *J. Org. Chem.* **2000**, *65*, 4261. (t) Bio, M. M.; Leighton, J. L. *Org. Lett.* **2000**, *2*, 2905. (u) Clive, D. L. J.; Sun, S.; Gagliardini, V.; Sano, M. K. *Tetrahedron Lett.* **2000**, *41*, 6259. (v) Yoshimitsu, T.; Yanagisawa, S.; Nagaoka, H. *Org. Lett.* **2000**, *2*, 3751. (w) Davies, H. M. L.; Ren, P. *Tetrahedron Lett.* **2000**, *41*, 9021. (x) For biosynthetic explorations, see: Spencer, P.; Agnelli, F.; Williams, H. J.; Keller, N. P.; Sulikowski, G. A. *J. Am. Chem. Soc.* **2000**, *122*, 420. (y) Njardarson, J. T.; Wood, J. L. *Org. Lett.*, in press. (z) Njardarson, J. T.; McDonlad, I. M.; Spiegel, D. A.; Inove, M.; Wood, J. L. *Org. Lett.* **2001**, *3*, 2435.

(3) For reviews, see: (a) Hepworth, D. *Chem. Ind. (London)* **2000**, *2*, 59. (b) Starr, J. T.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2000**, *39*, 1415. (c) Diederichsen, U. *Nachr. Chem. Tech. Lab.* **1999**, *47*, 1423.

(4) Nicolaou, K. C.; Vourloumis, D.; Winssinger, N.; Baran, P. S. *Angew. Chem., Int. Ed.* **2000**, *39*, 44.

Scheme 1. Model Studies and the Two Original Pathways toward the CP Central Core



synthesis.[6] Since then, three additional and elegant total syntheses have emerged from the Shair,[7] Fukuyama,[8] and Danishefsky[9] laboratories. In addition, numerous creative model studies toward these compounds have been reported.[2]

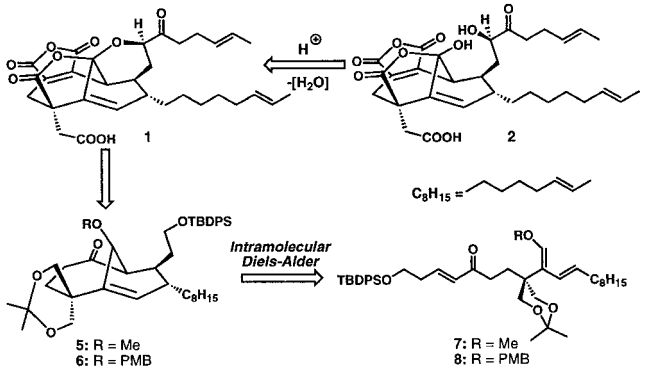
In this and the following two papers in this issue, we present a full account of our investigations, which led not only to the total syntheses of these molecules but also to a series of interesting discoveries including novel strategies, cascade reactions, and useful synthetic technologies.

We began our drive to the CP-molecules shortly after their disclosure[1a] and in 1997 reported two distinctly different approaches to model systems of their core skeleton (Scheme 1, paths A[2a] and B[2b]). While both paths (Scheme 1) featured novel reactions, the intramolecular Diels−Alder strategy was deemed more attractive due to higher overall yield and convergency, and was, therefore, adopted for full exploration as will be discussed below.

Results and Discussion

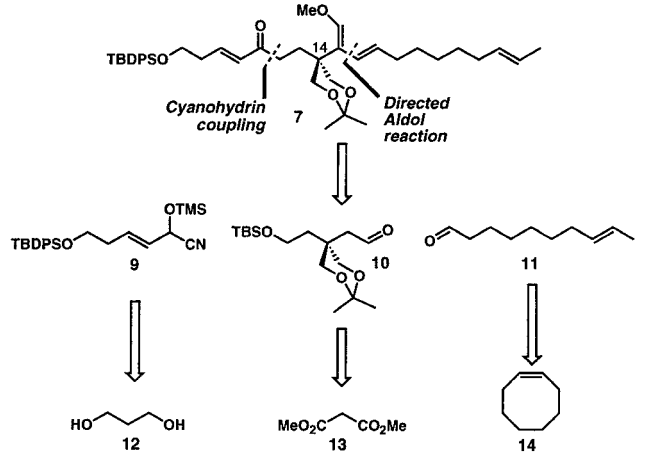
A simplified retrosynthetic analysis of the CP-molecules featuring the key Diels−Alder disconnection is illustrated in Scheme 2. We reasoned that construction and subsequent elaboration of an intermediate of type **7** or **8** could lead to the CP-molecules via a carefully orchestrated sequence. Our first-generation retrosynthesis of the precursor **7** to the bicyclo[4.3.1] skeleton of the CP-molecules via a type-II intramolecular Diels−Alder (IMDA)[10] reaction is shown in Scheme 3. This analysis featured a TMS−cyanohydrin coupling[11] and a directed Aldol reaction[12] to construct the key intermediate **7** from the simple

Scheme 2. Simplified Retrosynthetic Analysis of **1** and **2**[a]



[a] PMB = *p*-methoxybenzyl; TBDPS = *tert*-butyldiphenylsilyl.

Scheme 3. First-Generation Retrosynthetic Analysis of the Diels−Alder Precursor **7**

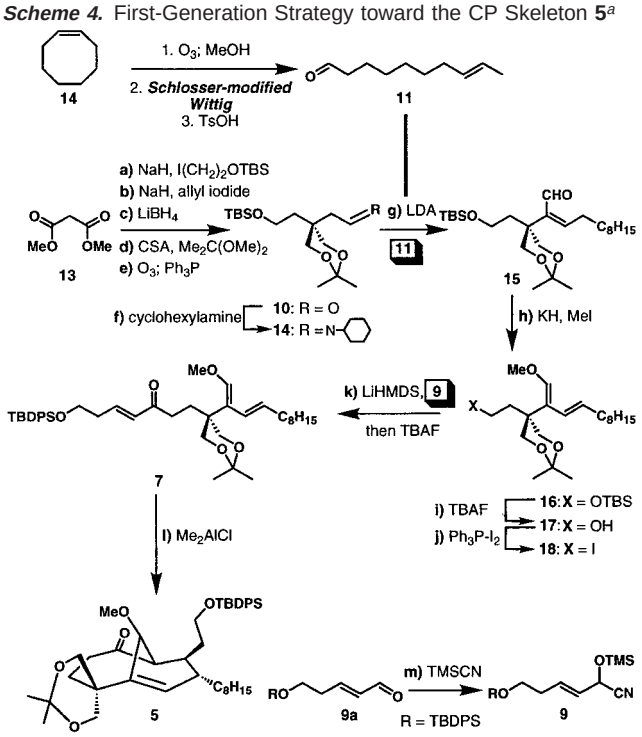


building blocks **9**−**11**. In turn, these building blocks, in principle, could be rapidly synthesized from inexpensive, commercially available propylene glycol (**12**), dimethyl malonate (**13**), and cyclooctene (**14**). This strategy was based on the successful model studies reported earlier on a simpler substrate (see Scheme 1) and included an important simplification with regards to the quaternary carbon.[2a] Thus, by proposing to enter the Diels−Alder reaction with a symmetrically substituted, prochiral quarternary center (C-14), we expected certain advantages. This belief was based on the reasoning that since the bicyclo[4.3.1] skeleton of **1** and **2** harbors pronounced concave and convex faces, the groups on C-14 could be differentiated with ease, later on.

1. Syntheses of Racemic Building Blocks. Scheme 4 summarizes the synthesis of the bicyclic core **5** in its racemic form. Thus, **13** was converted into aldehyde **10** via the five-step sequence entailing (i) treatment with NaH and quenching of the resulting anion with $I(CH_2)_2OTBS$ (60% yield), (ii) a second alkylation with NaH and allyl iodide (96% yield), (iii) reduction of both ester groups with $LiBH_4$ (72% yield), (iv) acetonide formation, and (v) ozonolysis, followed by reduction with Ph_3P (75% yield). Subsequent treatment of aldehyde **10** with cyclohexylamine under azeotropic removal of H_2O led to imine **14**. The directed Aldol reaction of imine **14** proceeded smoothly upon exposure to LDA at −20 °C, followed by quenching of the resulting anion with aldehyde **11** to afford, after acidic workup, α,β-unsaturated aldehyde **15** (ca. 1:1 mixture of geometric isomers) in 50% overall yield from **10**. Aldehyde **11** was expediently prepared, in two steps, from **14**

(5) (a) Part 1: Nicolaou, K. C.; Baran, P. S.; Zhong, Y.-L.; Choi, H.-S.; Yoon, W. H.; He, Y.; Fong, K. C. *Angew. Chem., Int. Ed.* **1999**, *38*, 1669. (b) Part 2: Nicolaou, K. C.; Baran, P. S.; Zhong, Y.-L.; Fong, K. C.; He, Y.; Yoon, W. H.; Choi, H.-S. *Angew. Chem., Int. Ed.* **1999**, *38*, 1676.
(6) Nicolaou, K. C.; Jung, J.-K.; Yoon, W. H.; He, Y.; Zhong, Y.-L.; Baran, P. S. *Angew. Chem., Int. Ed.* **2000**, *39*, 1829.
(7) Chuo, C.; Layton, M. E.; Sheehan, S. M.; Shair, M. D. *J. Am. Chem. Soc.* **2000**, *122*, 7424.
(8) Nobuaki, W.; Itoh, T.; Fukuyama, T. *J. Am. Chem. Soc.* **2000**, *122*, 7825.
(9) Tan, Q.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2000**, *39*, 4509.
(10) Bear, B. R.; Sparks, S. M.; Shea, K. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 820.
(11) Hertenstein, U.; Hünig, S.; Öller, M. *Chem. Ber.* **1980**, *113*, 3783.
(12) Wittig, G.; Reiff, H. *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 7.

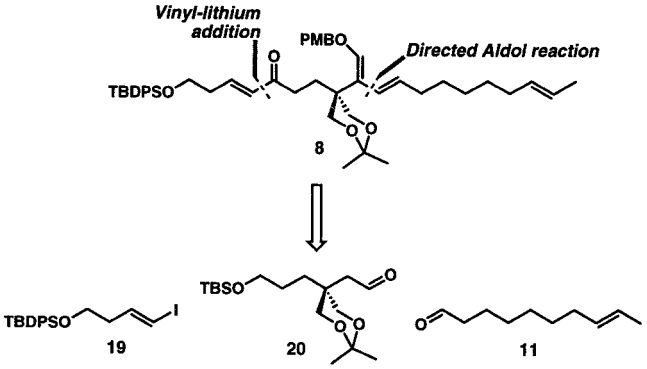
Scheme 4. First-Generation Strategy toward the CP Skeleton **5**[a]



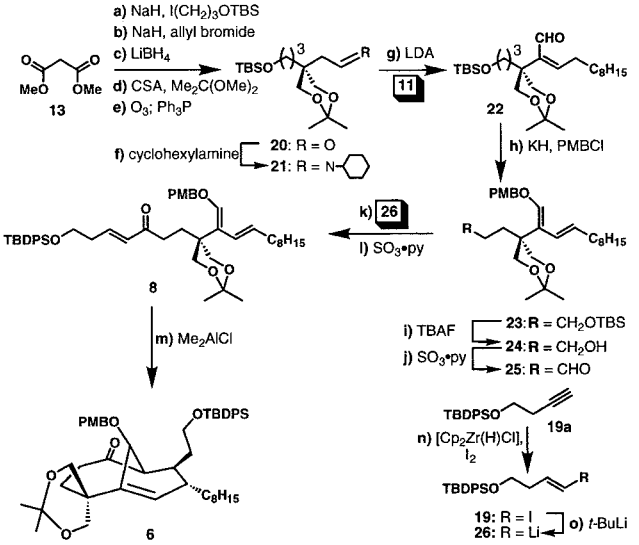
[a] Reagents and conditions: (a) NaH (1.3 equiv), $I(CH_2)_2OTBS$ (1.3 equiv), THF, reflux, 5 h; (b) allyl iodide (1.3 equiv), NaH (1.5 equiv), DME, 25 °C, 4 h, 96% overall; (c) $LiBH_4$ (2.0 equiv), THF, 0 → 25 °C, 2 h, 72%; (d) $Me_2C(OMe)_2$ (1.5 equiv), CSA (0.05 equiv), CH_2Cl_2, 25 °C, 10 min, 92%; (e) O_3, CH_2Cl_2, −78 °C, 1 h; then Me_2S (2.0 equiv), −78 → +25 °C, 12 h, 75%; (f) cyclohexylamine (1.2 equiv), benzene, Dean−Stark, 2 h; (g) LDA (1.1 equiv), Et_2O, −78 °C, 1 h; then $C_9H_{17}CHO$ (1.5 equiv) in Et_2O, −78 → 0 °C, 12 h; then oxalic acid (4.0 equiv), H_2O, 0 °C, 1 h, 50% overall from **10**; (h) KH (5.0 equiv), MeI (1.5 equiv), DME/HMPA (5:2), 0 °C, 1.2 h, 72%; (i) TBAF (2.0 equiv), THF, 0 °C, 2 h, 95%; (j) Ph_3P (1.8 equiv), imidazole (2.0 equiv), I_2 (1.5 equiv), CH_2Cl_2, 0 °C, 52%; (k) **9** (5.0 equiv), LiHMDS (5.0 equiv), THF, −78 °C, 0.5 h; then TBAF (3.0 equiv), 20 s, 39% overall; (l) Me_2AlCl (0.10 equiv), CH_2Cl_2, −10 °C, 0.5 h, 95%; (m) TMSCN (1.1 equiv), ZnI_2 (0.5 equiv), 25 °C, 12 h, 100%. TBS = *tert*-butyldimethylsilyl; DME = 1,2-dimethoxyethane; CSA = camphorsulfonic acid; LDA = lithium diisopropylamide; TBAF = tetra-*n*-butylammonium fluoride; DMF = *N*,*N*-dimethylformamide; LiHMDS = lithium hexamethyldisilazide; TMS = trimethylsilyl.

employing Schreiber's terminally differentiating ozonolysis methodology[13] (to produce the mono-dimethyl acetal aldehyde) followed by a Schlosser-modified Wittig reaction[14] and workup with TsOH to remove the initially installed dimethyl acetal. Exposure of **15** to KH followed by addition of MeI led to diene **16** as the sole isomer in 72% yield. In preparation for the next coupling, compound **16** was converted into the corresponding alkyl iodide (**18**) in 50% overall yield by desilylation with TBAF, and subsequent treatment of the resulting alcohol (**17**) with Ph_3P/I_2. Presumably as a consequence of the nearby quarternary center, nucleophilic acylation of **18** to afford the Diels−Alder precursor proceeded only sluggishly. Thus, conversion of cyanohydrin **9** to its anion with LHMDS or LDA, followed by addition of this anion to iodide **18** and workup with TBAF, afforded only ca. 25−40% yield of the desired coupling product **7**. Despite our inability to optimize this reaction, we were reassured by the fact that compound **7** underwent the expected intramolecular Diels−Alder reaction with ease in the presence of Me_2AlCl to afford the CP-molecule skeleton **5** in 95% yield. However, initial model studies to construct the various peripheral elements of the CP-molecules suggested that the methyl group could not serve as a suitable protecting group due to difficulties in its removal, and thus another approach was sought.

Scheme 5. Second-Generation Retrosynthetic Analysis of Diels−Alder Precursor **8**



Scheme 6. Second-Generation Synthesis of the Diels−Alder Product **6**[a]



[a] Reagents and conditions: (a) NaH (1.3 equiv), $I(CH_2)_3OTBS$ (1.3 equiv), THF, reflux, 5 h, 98%; (b) NaH (1.5 equiv), allyl bromide (1.3 equiv), DME, 25 °C, 4 h, 95%; (c) $LiBH_4$ (2.0 equiv), THF, 0 → 25 °C, 4 h, 87%; (d) $Me_2C(OMe)_2$ (1.5 equiv), CSA (0.05 equiv), CH_2Cl_2, 25 °C, 10 min, 94%; (e) O_3, CH_2Cl_2, −78 °C, 1 h; then Ph_3P (1.0 equiv), −78 → +25 °C, 12 h, 97%; (f) cyclohexylamine (1.2 equiv), benzene, reflux, Dean−Stark, 2 h; (g) LDA (1.1 equiv), Et_2O, −78 °C, 1 h; then $C_9H_{17}CHO$ (1.5 equiv) in Et_2O, −78 → +30 °C, 12 h; then oxalic acid (4.0 equiv), H_2O, 0 °C, 1 h, 80% overall from **20**; (h) KH (5.0 equiv), PMBCl (1.5 equiv), DME/HMPA (5:2), 0 °C, 15 min; (i) TBAF (2.0 equiv), THF, 25 °C, 2 h; (j) SO_3•py (3.0 equiv), Et_3N (5.0 equiv), CH_2Cl_2/DMSO (4:1), 0 → 25 °C, 3 h, 51% overall; (k) **26** (1.5 equiv), THF, −78 °C, 0.5 h; (l) SO_3•py (4.0 equiv), Et_3N (5.0 equiv), DMSO/CH_2Cl_2 (1:4), 25 °C, 3 h, 70% overall; (m) Me_2AlCl (0.02 equiv), CH_2Cl_2, −10 °C, 1 h, 90%; (n) $Cp_2Zr(H)Cl$ (1.2 equiv), **19a** (1.0 equiv), 25 °C, 3 h; then CCl_4, I_2 (1.0 equiv), 75%; (o) **19** (1.5 equiv), *t*-BuLi (1.5 equiv), THF, −78 °C, 0.5 h. PMB = *p*-methoxybenzyl chloride.

A second-generation strategy is illustrated retrosynthetically in Scheme 5. Whereas the first-generation approach involved displacement of a hindered iodide (**18**) with a hindered lithiocyanohydrin (**9**), the new strategy projected the union of two sterically unencumbered species (**25** and **26**, Scheme 6) derived from the building blocks **11**, **19**, and **20**. In addition, it was anticipated that the PMB group might be more versatile in

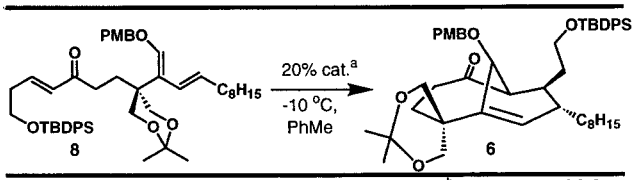
(13) Claus, R. E.; Schreiber, S. L. *Org. Synth.* **1986**, *64*, 150.
(14) Schlosser, M.; Christmann, K. F. *Liebigs Ann.* **1967**, *708*, 1.

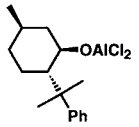
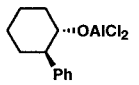
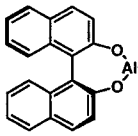
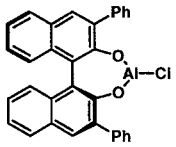
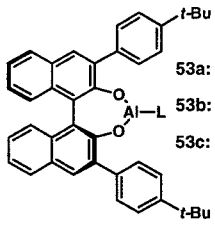
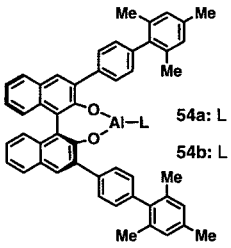
terms of orthogonality and stability to a range of reagents than the originally proposed methoxy group.

The construction of the Diels−Alder product **6** (racemic) from **13** is depicted in Scheme 6. Thus, reaction of **13** with NaH followed by quenching of the resulting enolate with $I(CH_2)_3$-OTBS led to pure monoalkylated malonate in 98% yield after flash chromatography. This compound was then treated with an additional equivalent of NaH in DME and quenched with allyl bromide (95% yield). Reduction of the ester groups of the resulting dialkylated product with $LiBH_4$ in THF and protection of the resulting 1,3-diol as the acetonide by exposure to 2,2-dimethoxypropane and catalytic amounts of CSA in CH_2Cl_2 led to aldehyde **20** after ozonolytic cleavage of the terminal olefin, in 78% yield overall yield. Initial attempts to construct diene **23** from aldehyde **20** were plagued by the formation of large amounts of the undesired *E*,*E*-diene isomer. Not surprisingly, the latter diene, when carried through the remainder of the sequence (to generate the *E*,*E*-isomer of **8**), failed to participate in the key Diels−Alder ring closure. After much experimentation, the desired *E*,*Z*-diene **23** was delivered stereoselectively from **22** by a carefully controlled sequence involving treatment with KH followed by syringe pump addition of PMBCl in DME to the resulting anion at 0 °C over 1 h. Alternative solvents, temperatures, and orders of addition had a deleterious effect on the ratio of dienes formed as did the quality of the reagents (KH and PMBCl) employed. In preparation for the key vinyllithium addition, compound **23** (crude) was treated with TBAF to remove the TBS group, and the resulting alcohol (**24**) was oxidized to the corresponding aldehyde (**25**) with SO_3•py in 51% overall yield from **20**. Addition of **25** to a solution of vinyllithium **26** (prepared from the corresponding iodide **19** and *n*-BuLi, Scheme 6) led to the expected allylic alcohol, which was quickly oxidized (SO_3•py) to the α,β-unsaturated ketone **8** in 70% overall yield. The planned type-II intramolecular Diels−Alder reaction was then accomplished upon exposure of the latter compound (**8**) to Me_2AlCl at −10 °C, forming, within minutes, the desired [4.3.1] bicyclic ketone **6** in 90% yield.

2. Asymmetric Synthesis of Building Blocks. Attempts by us and others to crystallize naturally derived heavy-atom derivatives of the CP-molecules to decipher their absolute configuration via X-ray crystallographic analysis have been thwarted by the inability to grow suitably ordered crystals. We, therefore, turned our attention to determining the absolute configuration of these compounds through chemical synthesis. Toward this end, a chiral reagent-based strategy was originally designed for the synthesis of enantiomerically enriched building blocks for the CP total synthesis. The obvious stage to evaluate this strategy was at the key Diels−Alder cyclization, which could, in principle, be induced by chiral catalysts. As shown in Table 1, despite the use of numerous chiral Lewis acid catalysts, only marginal success was realized. The low levels of enantioselectivity in this reaction were attributed to the monodentate nature of the dienophile moiety and the flexibility of the aluminum−oxygen coordination bond of the initially formed complex between the substrate and the Lewis acid. In view of these disappointing results, a strategy predicated on substrate-based control of the diastereoselectivity of the cycloaddition was then undertaken. Specifically, we envisaged modifying the ketone precursor **8** to introduce a bulky chiral moiety capable of influencing the facial selectivity of the key Diels−Alder reaction. An additional design criterion was that the Diels−Alder precursor could be seamlessly converted into a known intermediate along the path chartered for the total syntheses of the racemic compounds. Since the absolute configurations of **1** and **2** were unknown, we arbitrarily chose the chirality of the starting material and then proceeded to identify optimum substrates/conditions for a diastereoselective cycloaddition and to rigorously determine the absolute configurations of the resulting intermediates before finally carrying the optically enriched compounds through the previously developed sequence to the CP-molecules.

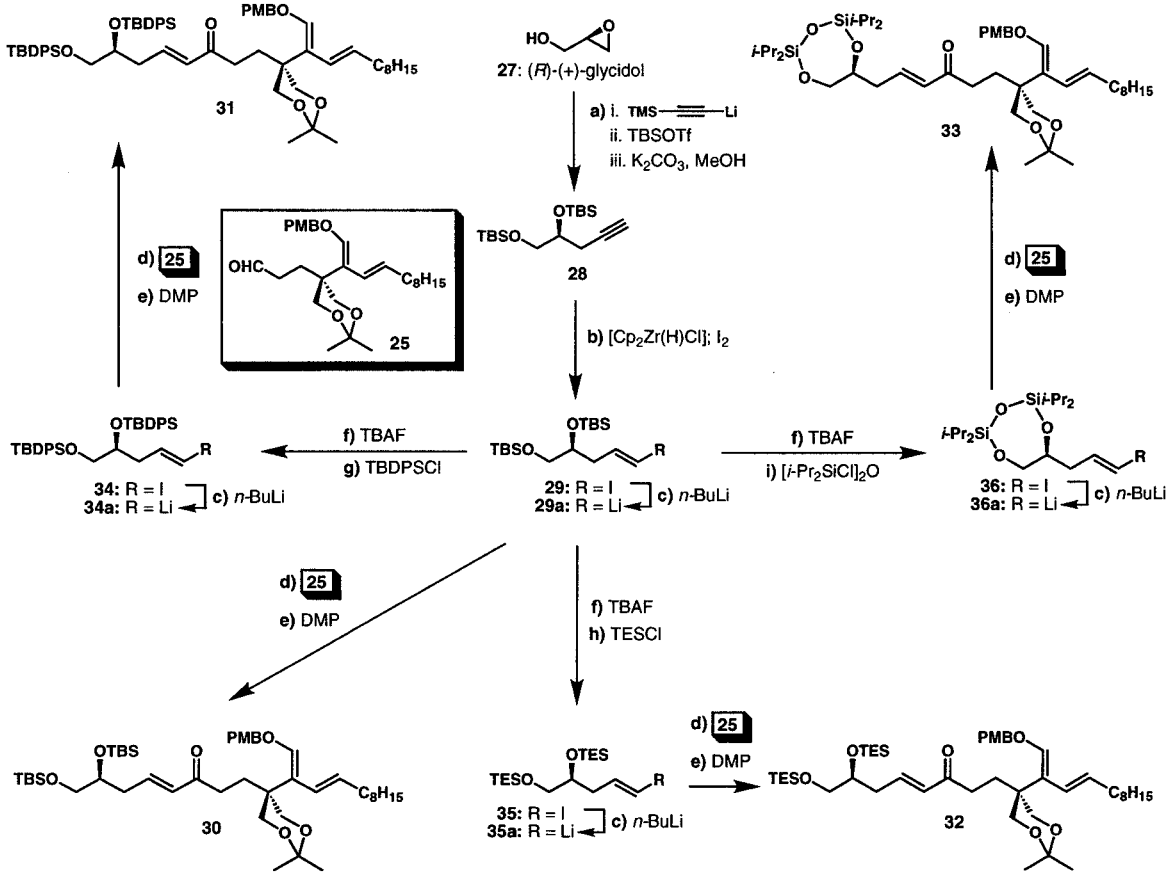
Table 1. Asymmetric Induction in the Diels−Alder Reaction of Prochiral Triene Compound **8** in the Presence of Enantiomerically Enriched Lewis Acid Catalysts



Entry	Catalyst	Yield(%)[b]	ee(%)(+ or -)[c]	$[\alpha]_D$
1	 **49**	85	0	0[d]
2	 **50**	79	1.5 (-)	-1.6[d]
3	 **51a:** L = Cl	74	6 (-)	-4.2[d]
4	**51b:** L = Me	82	6 (+)	+4.2[e]
5	 **52**	85	8 (-)	-6.9[f]
6	 **53a:** L = Cl	87	10 (-)	-6.8[g]
7	**53b:** L = Me	79	16 (+)	+10.9[h]
8	**53c:** L = *i*-Bu	82	20 (+)	+13.8[i]
9	 **54a:** L = Cl	77	14 (-)	-10.0[j]
10	**54b:** L = *i*-Bu	84	1 (+)	+0.6[k]

[a] Reactions carried out with 0.02 mmol of substrate (**8**) in toluene (1.5 mL). [b] Isolated, chromatographically pure **6**. [c] Enantiomeric excess was determined by analysis of the desilylated product using chiral HPLC (ChiralCel OD, *i*-PrOH/hexanes (7:93), flow rate 0.5 mL/min, detection wavelength 254 nm). [d] $c = 1.0$, $CHCl_3$. [e] $c = 0.8$, $CHCl_3$. [f] $c = 0.36$, $CHCl_3$. [g] $c = 0.77$, $CHCl_3$. [h] $c = 0.75$, $CHCl_3$. [i] $c = 0.73$, $CHCl_3$. [j] $c = 0.25$, $CHCl_3$. [k] $c = 0.52$, $CHCl_3$.

Scheme 7. Synthesis of Enantiomerically Enriched Diels−Alder Precursors **30**−**33**[a]



[a] Reagents and conditions: (a) (i) TMSC≡CH (1.5 equiv), *n*-BuLi (1.4 equiv), THF, −78 °C, added to a solution of **27** (1.0 equiv), *n*-BuLi (1.1 equiv), THF, −78 → +25 °C, 12 h; (ii) TBSOTf (3.0 equiv), 2,6-lutidine (1.0 equiv), CH_2Cl_2, 0 to 25 °C; (iii) K_2CO_3 (2.0 equiv), MeOH, 25 °C, 12 h; (b) $Cp_2Zr(H)Cl$ (1.2 equiv), benzene, 25 °C; then I_2 (1.0 equiv), CCl_4, 25 °C, 62% overall from **27**; (c) vinyl iodide (1.5 equiv), *n*-BuLi (1.5 equiv), THF, −78 °C, 0.5 h; (d) vinyl iodide added to **25** in THF, −78 °C, 0.5 h, 90%; (e) DMP (1.3 equiv), $NaHCO_3$ (5.0 equiv), CH_2Cl_2, 25 °C, 1 h, 49% (**30**), 64% (**31**), 56% (**32**); (f) TBAF (4.0 equiv), THF, 25 °C, 2 h; (g) TBDPSCl (3.5 equiv), imidazole (4.0 equiv), 20 h, 85%; (h) TESCl (3.5 equiv), imidazole (4.0 equiv), CH_2Cl_2, 25 °C, 20 h, 90%; (i) [*i*-$Pr_2SiCl]_2O$ (2.0 equiv), imidazole (3.0 equiv), CH_2Cl_2, 25 °C, 20 h, 86%.

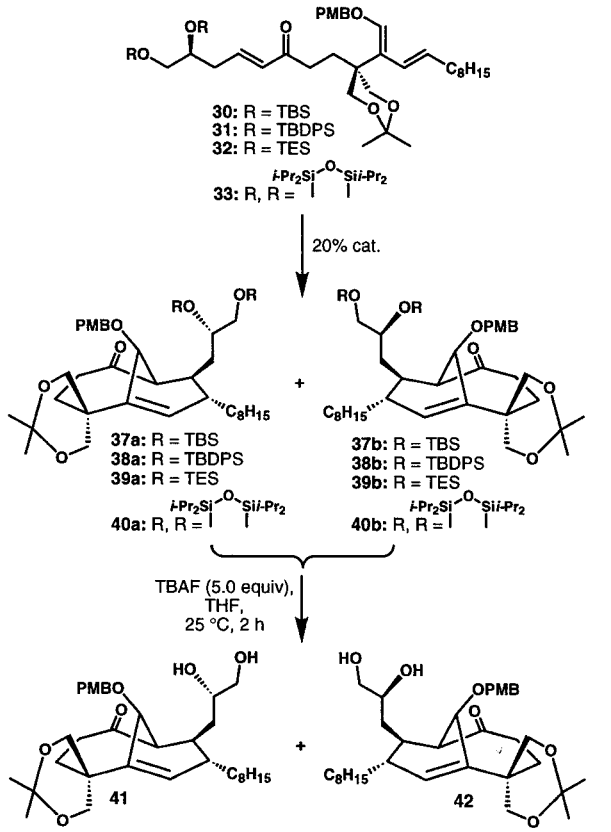
With these considerations in mind, we embarked on the synthesis of a variety of chiral Diels−Alder precursors as depicted in Scheme 7. Thus, the *di*silyl acetylene **28** served as the key building block for the construction of a variety of different chiral ketones (**30**−**33**). This compound (**28**) was prepared from the arbitrarily chosen (*R*)-glycidol (**27**) by sequential epoxide opening with TMS acetylide, addition of TBSOTf, and selective removal of the pendant TMS group (K_2CO_3, MeOH) (62% yield overall). Exposure of **28** to the Schwartz reagent[15] [$Cp_2Zr(H)Cl$] followed by addition of I_2 then led to the vinyl iodide **29** in 72% overall yield. Metal−halogen exchange (*n*-BuLi) facilitated the union of the vinyl iodide **29** with the previously synthesized aldehyde **25**, furnishing, after oxidation with SO_3•py, enone−diene **30** (49% yield overall) via the lithio derivative **29a**. Alternatively, the silyl protecting groups of vinyl iodide **29** could be exchanged upon treatment with TBAF and reprotection of the resulting diol with the corresponding silyl chloride (TBDPSCl, TESCl, or [*i*-$Pr_2SiCl]_2O$) to afford vinyl iodides **34**−**36**, respectively. Enone−dienes **31**−**33** were then similarly prepared from these vinyl iodides employing the same chemistry as for the preparation of **30** (see Scheme 7).

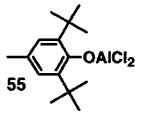
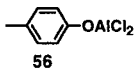
All four precursors (**30**−**33**) were subjected to intramolecular Diels−Alder reactions in the presence of various chiral catalysts. As illustrated in Table 2, the structure of the Lewis acid employed as a catalyst had only a moderate effect on the diastereoselectivity of the intramolecular Diels−Alder reaction. Strikingly, neither antipode of the bulky catalyst **53a** (see Table 1) had much influence on the cyclization (entries 1 and 2, Table 2) as compared to Et_2AlCl itself (entry 5, Table 2). However, when the bis(TBS) ketone **30** was employed, optimum conditions were found whereby the use of catalyst **55** in toluene at −80 °C gave a ca. 5.7:1 mixture of diastereomeric Diels−Alder products **37a** and **37b**. The TBDPS-, TES-, and cyclic silyl-protected ketones (**31**, **32**, and **33**, respectively) led, under similar conditions, to lower diastereoselectivities (entries 7−11, Table 2) as compared to bis(TBS) ketone **30**. Incidentally, when the diol derived from enone **30** with TBAF was treated with catalytic amounts of Et_2AlCl, rapid decomposition was observed.

Satisfied with the selectivity achieved using catalyst **55** with triene **30**, we proceeded to determine the absolute configurations of the major and minor diastereomers (**37a** and **37b**, Table 2, chromatographically separated) resulting from the Diels−Alder reaction. Toward this end, and as shown in Scheme 8, **37a** and **37b** were converted separately to the α-methoxy ketones **45a** and **45b**, respectively, for comparison purposes with an authentic racemic sample of **46**.[16] Thus, the major isomer **37a** was treated with TBAF to remove both TBS groups (95% yield) followed by selective reprotection of the primary hydroxyl group with

(15) Schwartz, J.; Labinger, J. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 333.

Table 2. Diastereomeric Induction in the Diels–Alder Reaction of the Enantiomerically Enriched Compounds **30**–**33** in the Presence of Optically Enriched Lewis Acid Catalysts

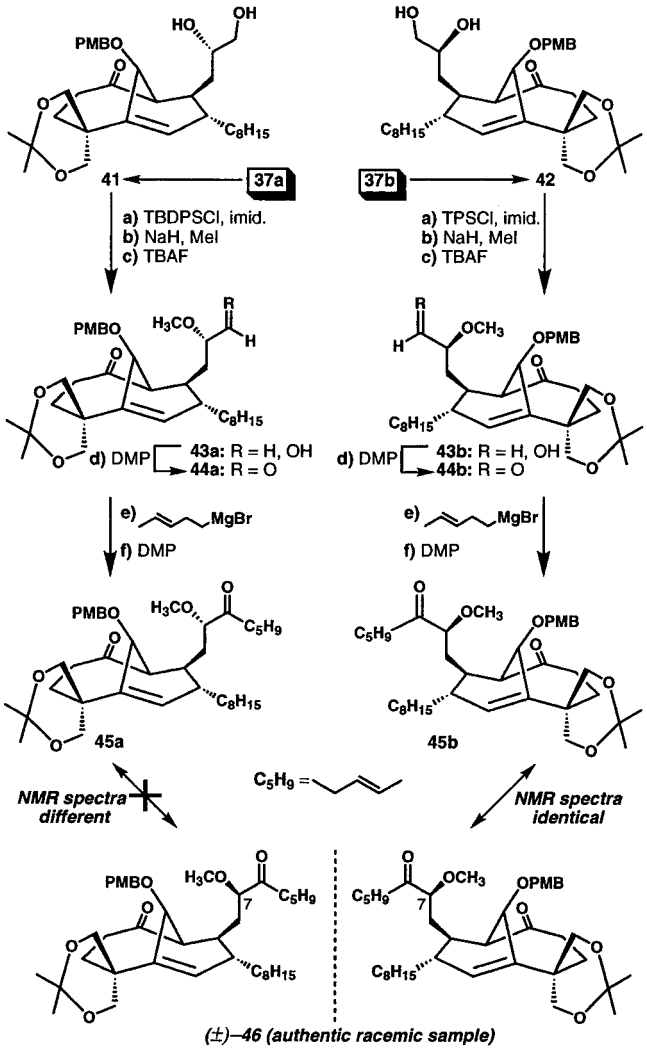


Entry	Compound	Catalyst[a]	Conditions	Yield (%)[b]	Ratio (a:b)[c]
1	**30**	(*S*) - **53a**	PhMe, -30 °C	90	3.2:1
2	**30**	(*R*) - **53a**	PhMe, -30 °C	88	2.5:1
3	**30**	 **55**	CH_2Cl_2, -80 °C	85	4.5:1
4	**30**	**55**	PhMe, -80 °C	88	5.7:1
5	**30**	Et_2AlCl	CH_2Cl_2, -10 °C	82	2:1
6	**30**	 **56**	PhMe, -80 °C	75	4.5:1
7	**31**	Et_2AlCl	CH_2Cl_2, 0 °C	81	1:1
8	**31**	**55**	PhMe, -70 °C	85	1:1
9	**31**	(*S*) - **53a**	PhMe, -30 °C	89	1.2:1
10	**32**	**55**	PhMe, -80 °C	71	3.1:1
11	**33**	**55**	PhMe, -80 °C	73	4.6:1

[a] For the structures of the catalysts, see Table 1. [b] Isolated yield of chromatographically pure compounds. [c] Determined by ^{1}H NMR spectroscopy.

TBDPSCl (96% yield). Protection of the remaining secondary alcohol with MeI (NaH, THF, 0 °C, 51% yield) and removal of the TBDPS group led to alcohol **43a** in 91% overall yield. DMP-mediated oxidation of the latter compound (**43a**) followed

Scheme 8. Conversion of Enantiomerically Enriched Diels–Alder Products **37a** and **37b** to Intermediates **45a** and **45b** and Comparisons with Authentic Racemic Sample **46**[a]

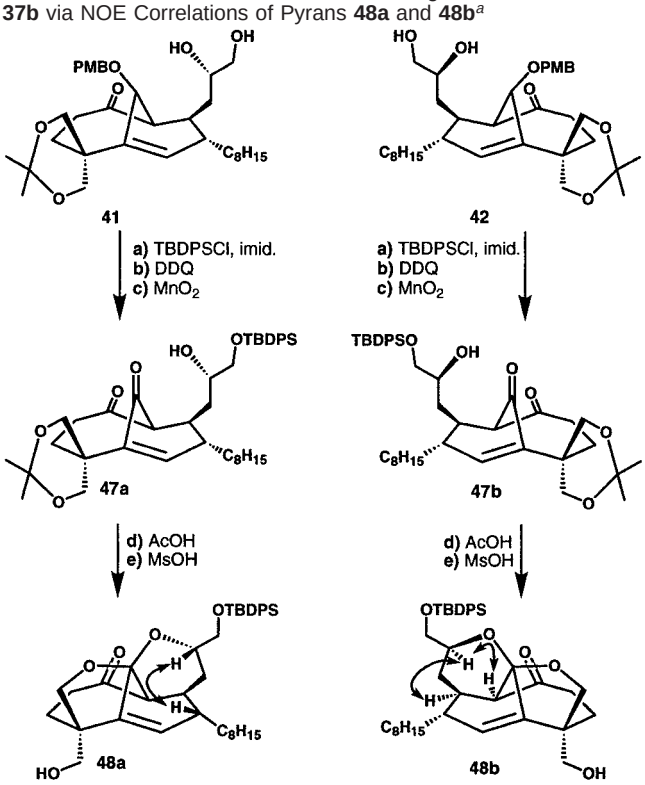


[a] Reagents and conditions: (a) TBDPSCl (2.0 equiv), imidazole (2.1 equiv), CH_2Cl_2, 0 °C, 1 h, 96%; (b) NaH (4.1 equiv), MeI (4.1 equiv), 0 °C, 1 h, 51%; (c) TBAF (excess), THF, 0 to 25 °C, 2 h, 91% (47% overall for **43b**); (d) DMP (2.0 equiv), $NaHCO_3$, CH_2Cl_2, 25 °C; (e) 3-pentenylmagnesium bromide (1.25 equiv), THF, −78 °C, 1 min; (f) DMP (2.0 equiv), $NaHCO_3$ (2.0 equiv), CH_2Cl_2, 25 °C, 64% (48% overall for **43b**). DMP = Dess–Martin periodinane.

by chemoselective attack on the resulting aldehyde **44a** with C_5H_9MgBr (see Scheme 8) led to the α-methoxy ketone **45a** (64% yield), whose ^{1}H and ^{13}C NMR spectra were different from those of racemic **46**. The minor product **37b** was carried through the same seven-step sequence to furnish **45b**, which proved to be identical with **46** by ^{1}H and ^{13}C NMR spectroscopy. Because the configuration of C-7 in the racemic sample **46** was verified, it followed that the major product **37a** had the absolute configuration shown in Scheme 8. An independent proof of the stereochemistry of diastereomers **41** and **42** (derived from **37b**) was also carried out as summarized in Scheme 9. Thus, a TBDPS group was selectively installed (TBDPSCl, imidazole, 96% yield) on the primary hydroxyl groups of **41** and **42**, and the PMB group was removed by treatment with DDQ (44% yield). The resulting allylic alcohols were oxidized with MnO_2

(16) Nicolaou, K. C.; Baran, P. S.; Zhong, Y.-L.; Fong, K. C.; Choi, H.-S. *J. Am. Chem. Soc.* **2002**, *124*, 2190–2201.

Scheme 9. Verification of the Absolute Configuration of **37a** and **37b** via NOE Correlations of Pyrans **48a** and **48b**[a]



[a] Reagents and conditions: (a) TBDPSCl (2.0 equiv), imidazole (2.1 equiv), CH_2Cl_2, 0 °C, 1 h, 96%; (b) DDQ (2.1 equiv), CH_2Cl_2/H_2O (20:1), 25 °C, 2 h, 44%; (c) MnO_2 (excess), CH_2Cl_2, 25 °C, 74% (30% overall yield of **47b** from **42**); (d) 80% aqueous AcOH, 60 °C, 3 h; (e) CH_3SO_3H (catalytic), CH_2Cl_2, 1 h, 70% (67% overall for **48b**).

to afford the bridgehead enones **47a** and **47b** (74% yield). Sequential treatment of **47a** and **47b** with AcOH (to remove the acetonide with simultaneous formation of the hemiketal and $MeSO_3H$ to effect dehydrative ring closure)[1] furnished the rigid pyran systems **48a** and **48b** (70% overall yield). The observed NOEs (see arrows on structures **48a** and **48b**, Scheme 9) in these compounds confirmed the initial assignment.

Conclusion

The chemistry described herein laid the foundation for the total syntheses of both racemic and enantiomerically pure CP-molecules (**1** and **2**). Specifically, the efficient and stereoselective pathway to the bicyclo[4.3.1] ketone **6** containing the basic CP core and enough oxygen atoms for eventual elaboration to the target molecules was chartered. Furthermore, an asymmetric approach to suitable optically active building blocks (**37a** and **37b**) was developed. The application of this chemistry to the total syntheses of the CP-molecules and the determination of their absolute stereochemistry will be the subject of the following two papers in this series.[16,17]

Acknowledgment. We thank Drs. D. H. Huang and G. Siuzdak for NMR spectroscopic and mass spectrometric assistance, respectively. This work was financially supported by the National Institutes of Health, The Skaggs Institute for Chemical Biology, doctoral fellowships from the National Science Foundation (to P.S.B.) and Boehringer Ingelheim (to Y.H.), a postdoctoral fellowship from the Korea Science and Engineering Foundation (to H.-S.C.), and grants from Abbott, Amgen, ArrayBiopharma, Boehringer Ingelheim, DuPont, Glaxo, Hoffmann-La Roche, Merck, Pfizer, and Schering Plough.

Supporting Information Available: Experimental procedures and compound characterization (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA012010L

(17) Nicolaou, K. C.; Zhong, Y.-L.; Baran, P. S.; Jung, J.; Choi, H.-C.; Yoon, W. H. *J. Am. Chem. Soc.* **2002**, *124*, 2202−2211.