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Total Synthesis of (+)-Acanthodoral by the Use of a Pd-Catalyzed Metal-ene Reaction and a Nonreductive 5-*exo*-Acyl Radical Cyclization

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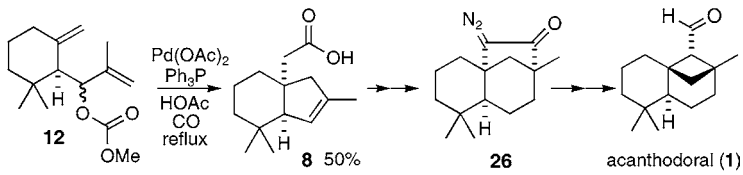
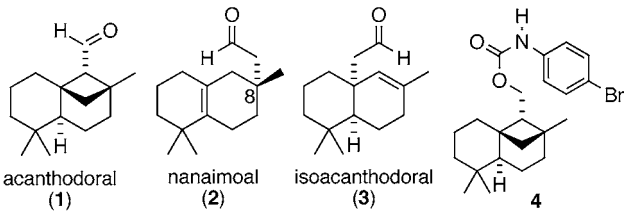
ABSTRACT



The first total synthesis of the antibiotic acanthodoral (1) has been achieved from 3-methyl-2-cyclohexen-1-one in 19 steps in 2.1% overall yield. The synthesis features the use of a Pd-ene reaction in the presence of CO to form the endocyclic alkene 8, a nonreductive acyl radical cyclization reaction, and a ring contraction reaction by the Wolff rearrangement. (+)-Acanthodoral has also been synthesized starting from (+)-*S*-2,2-dimethyl-6-methylenecyclohexanecarboxylic acid.

As in the case of countless secondary metabolites produced by other marine organisms,[1] those from the dorid nudibranchs *Acanthodoris nanaimoensis* include terpenoids with unprecedented carbon skeletons.[2]

Of these, the structure of acanthodoral (**1**) contains the highly strained bicyclo[3.1.1]heptane framework. Although acanthodoral contaminated with the other two coexisting sesquiterpene aldehydes **2** and **3** was shown to exhibit strong antibiotic activity, the inherent activity of acanthodoral itself could not be assessed due to the difficulty in its isolation in pure form.[2] The structure and relative stereochemistry of acanthodoral were established by the X-ray analysis of the urethane derivative, **4**.[2] Although its optical rotation has not been determined, on the basis of biosynthetic studies demonstrating that acanthodoral is derived from nanaimoal (**2**) and/or isoacanthodoral (**3**), the absolute stereochemistry of acanthodoral was postulated as shown for structure **1**.[2,3] The absolute stereochemistry at C-8 of nanaimoal (**2**) has been validated as R by its total synthesis from a compound with a known configuration.[4,5]



In connection with our continued interest in the development of approaches toward the synthesis of strained natural products, we set out to investigate the total synthesis of acanthodoral (**1**).[6,7] Our initial attempts at directly construct-

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(1) For a recent review, see: Blunt, J. W.; Copp, B. R.; Munro, M. H. G.; Northcote, P. T.; Prinsep, M. R. *Nat. Prod. Rep.* **2003**, *20*, 1−48.
(2) (a) Ayer, S. W.; Andersen, R. J.; He, C. H.; Clardy, J. *J. Org. Chem.* **1984**, *49*, 2653−2654. (b) Ayer, S. W. Ph.D. Thesis, University of British Columbia, 1985.
(3) Graziani, E. I.; Andersen, R. J. *J. Am. Chem. Soc.* **1996**, *118*, 4701−4702.
(4) Ayer, S. W.; Hellou, J.; Tischler, M.; Andersen, R. J. *Tetrahedron Lett.* **1984**, *25*, 141−144.
(5) Omodani, T.; Shishido, K. *J. Chem. Soc., Chem. Commun.* **1994**, 2781−2782.

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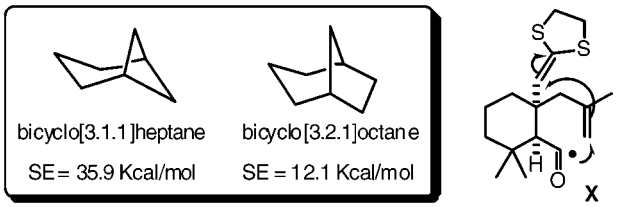
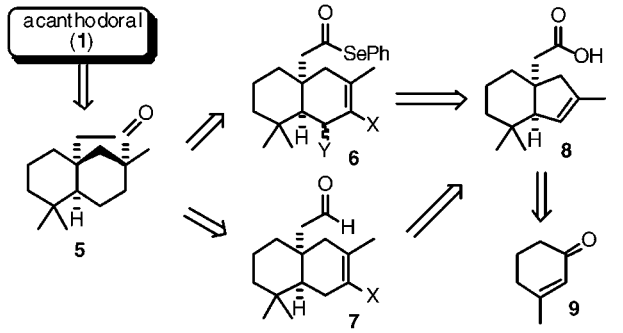
ing the bicyclo[3.1.1]heptane system by a tandem 6-*endo*-acyl radical/4-*exo*-alkyl radical cyclization sequence (see, e.g., structure **X** above) were not successful presumably due to its insurmountably severe strain energy (SE).[8] We, therefore, opted for an indirect approach that involves initial assembly of the substantially less strained bicyclo[3.2.1]-octane system followed by a ring contraction to the desired bicyclo[3.1.1]heptane system.



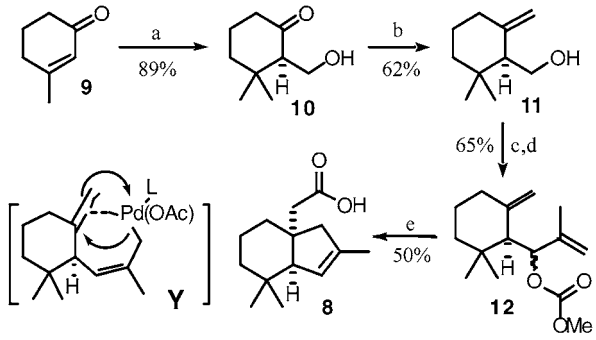
As summarized in the retrosynthetic analysis (Scheme 1), tricyclic ketone **5** is converted into acanthodoral using a Wolff rearrangement reaction.[9] The synthesis of ketone **5** was envisaged as being obtainable from either **6** by a nonreductive acyl radical recyclization[10] or **7** by an intramolecular Prins reaction.[11] The intermediates **6** and **7** could readily be accessed from hydrindene acid **8** by ring expansion of its dibromocyclopropane derivative. Hydrindene acid **8** in turn was predicted to be prepared by the use of a palladium-mediated metal ene-reaction.

Scheme 1. Retrosynthetic Analysis of Acanthodoral (**1**)



The key intermediate acid **8** was synthesized starting from 3-methyl-2-cyclohexen-1-one (**9**) in five steps (Scheme 2). Alkenol **11** obtained from ketone **10** by the Takai/Oshima-Lombardo methylenation[12] was transformed into the methyl

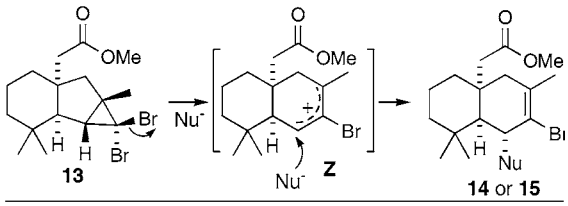
Scheme 2. Synthesis of Hydrindene Carboxylic Acid **8**[a]



[a] Reagents and conditions: (a) MeMgBr (1.2 mol equiv), CuI (0.05 mol equiv), LiCl (0.1 mol equiv)/THF, 0 °C, 0.5 h, then CH_2O (gas), −15 °C, 0.5 h; (b) CH_2Br_2/Zn/$TiCl_4$ (1:3:0.7 molar ratio) (excess)/CH_2Cl_2, rt, 0.5 h; (c) Swern oxidation; (d) isopropenylmagnesium bromide (2 mol equiv)/THF, 0 °C, then HMPA (20% v/v), $ClCO_2Me$ (2.2 mol equiv); 0 °C → rt; (e) $Pd(OAc)_2$ (0.1 mol equiv), PPh_3 (0.4 mol equiv)/HOAc, CO (1 atm), reflux, 12 h.

carbonate **12**. Treatment of carbonate **12** with $Pd(OAc)_2$/Ph_3P in wet acetic acid at 118 °C under CO[13] resulted in the formation of the five-membered *endo*-alkene acid **8** in 50% yield. The reaction may be viewed as a Pd-mediated metalene reaction, and it is likely to proceed through the σ-allyl complex intermediate **Y** (see Scheme 2).[14,15]

The ring expansion of the hydrindene to the 6,6-cis-fused, functionalized decalin system was achieved by the solvolysis of the *gem*-dibromocyclopropane derivative **13**, which in turn was prepared from acid **8** in two steps [(1) K_2CO_3, MeI/acetone, rt (92%); (2) $CHBr_3$, CH_2Cl_2, $BnEt_3NCl$, rt, 50% aq NaOH]. Thus, simply exposing **13** to a sulfur (**16** or **17**) or hydride nucleophile (Et_3SiH) in $(CF_3)_2CHOH$[16] resulted in the stereo- and regioselective formation of the corresponding decalin product in excellent yield, presumably via the π-allylic cation intermediate **Z** (Figure 1). Interestingly, use of an Ag^+ salt[17] led to the formation of complex mixtures of products.



nucleophile	conditions	product (yield)
H-S–(CH₂)₂–C(=O)OMe (**16**)	CF_3CH_2OH, rt, 2 d	**14** (50%)
	$(CF_3)_2CHOH$, rt, 8 h	**14** (83%)
H-S–C₆H₄–OMe (**17**)	$(CF_3)_2CHOH$, $NaHCO_3$ rt, 4 h	**14** (94%)
Et_3Si-H ($Nu^- = H^-$)	$(CF_3)_2CHOH$, $NaHCO_3$ rt, 12 h	**15** (99%)

Figure 1. Construction of the Decalin System from **13**.

(6) See, e.g.: Zhang, L.; Koreeda, M. *Org. Lett.* **2002**, *4*, 3755−3758.
(7) For a previous synthetic study toward acanthodoral, see: Engler, T. A.; Ali, M. H.; Takusagawa, F. *J. Org. Chem.* **1996**, *61*, 8456−8463.
(8) Liebman, J. F.; Greenberg, A. *Chem. Rev.* **1976**, *76*, 311−365.
(9) Reviews: (a) Gill, G. B. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, UK, 1991; Vol. 3, pp 887−912. (b) Ye, T.; McKervey, M. A. *Chem. Rev.* **1994**, *94*, 1091−1160. (c) Kirmse, W. *Eur. J. Org. Chem.* **2002**, 2193−2256.
(10) Review: Chatgilialoglu, C.; Crich, D.; Komatsu, M.; Ryu, I. *Chem. Rev.* **1999**, *99*, 1991−2069.
(11) Reviews: (a) Adams, D. R.; Bhatnagar, S. P. *Synthesis* **1977**, 661−672. (b) Snider, B. B. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.: Pergamon Press: Oxford, UK., 1991; Vol. 2, pp 661−672.

In an effort to access the bicyclo[3.2.1]octane skeleton by an intramolecular Prins reaction, aldehyde **18**, obtained from **15** in two steps ((1) $LiAlH_4$; (2) Dess−Martin periodinane) in 95% overall yield, was treated with a catalytic amount of Et_2AlCl in CH_2Cl_2 at room temperature (Figure 2). While

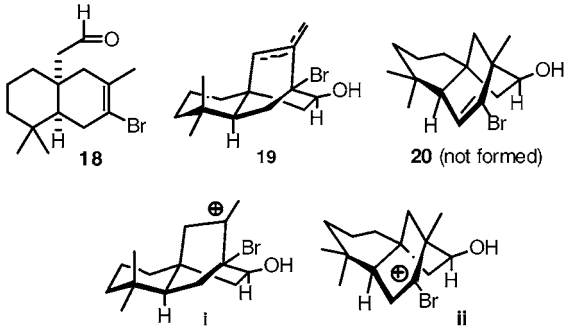
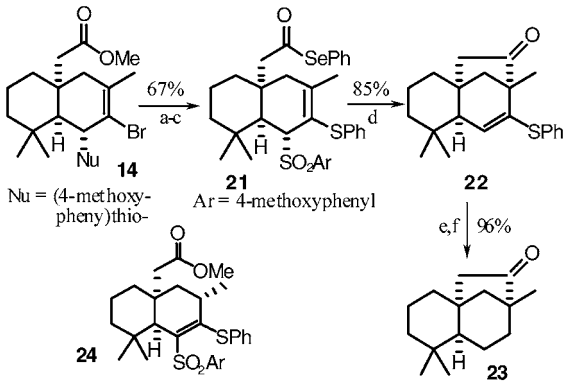


Figure 2. Prins Reaction of Aldehyde **18**.

the reaction produced the bicyclo[2.2.2]octane **19** as a 9:1 regioisomeric alkene mixture in 90% yield within 30 min, favoring the endocyclic alkene, the formation of the desired tricyclic alcohol with the bicyclo[3.2.1]octane skeleton, **20**, was not observed. In view of the similar SEs of these two bicyclooctane systems,[8] exclusive formation of **19** may be attributable, at least partially, to the relative carbocation-stabilizing abilities of the methyl and bromine groups in intermediates **i** and **ii**, respectively.[18]

Our efforts were then directed to the use of a nonreductive acyl radical cyclization to construct the bicyclo[3.2.1]octane skeleton, **23**. To obviate the complications resulting from the direct interaction between the acyl radical and the S atom introduced as a nucleophile during the solvolysis reaction of **13**, the 4-methoxyphenyl sulfide in **14** was first oxidized to the corresponding sulfone (Scheme 3). In addition, it was envisaged that, in view of the electrophilic nature of an acyl radical, the presence of a bromine atom should make the radical cyclization less favorable, and a means of replacing the Br with an electron-donating group was sought. This group would also have to be readily reductively removable.

Scheme 3. Synthesis of Tricyclic Ketone **23**[a]



[a] Reagents and conditions: (a) MCPBA (2.3 mol equiv)/CH_2Cl_2, rt, 4 h (97%); (b) 50% aq NaOH (8/1), PhSH (4 mol equiv), reflux, 6 h (99%); (c) $PhOP(=O)Cl_2$ (2 mol equiv), Et_3N (3 mol equiv), 0 °C, 1 h, then PhSeH (3 mol equiv)/Et_3N (5 mol equiv), 0 °C, 0.5 h (70%); (d) $(Bu_3Sn)_2$ (2 mol equiv)/PhH, sun lamp, reflux, 2 h; (e) Raney nickel/MeOH, −20 °C, 5 min; (f) H_2 (55 psi), PtO_2 (cat)/EtOAc, 2.5 h.

Fortuitously, during an attempt to hydrolyze the methyl ester of **14** with the 4-methoxyphenyl sulfone group (MeOH, aq NaOH, reflux), it was observed that the bromine atom was replaced with a methoxyl group in addition to hydrolysis of the methyl ester. This presumably involved deprotonation of the α-H to the sulfonyl group followed by replacement of the Br with MeO in the vinyl sulfone intermediate. Treatment of the sulfone obtained from sulfide **14** [Nu = 4-(MeO)PhS−] with PhSH under basic conditions resulted in quantitative formation of the hydrolysis product with the Br cleanly replaced by the PhS group (Scheme 3). Interestingly, as in the case of using MeO^- as the nucleophile, the corresponding conjugated sulfone **24** was not observed. As expected, the acyl radical generated from seleno ester **21** under nonreductive conditions underwent regioselective cyclization to provide tricyclic ketone **22** with a bicyclo-[3.2.1]octane framework. This was subsequently transformed into tricyclic ketone **23**.

The elaboration of the tricyclic ketone **23** into acanthodoral (**1**) was achieved by the Wolff rearrangement reaction of α-diazoketone **26** (Scheme 4), which was prepared from α-oxime ketone **25**. Treatment of ketone **23** with isoamyl nitrite in the presence of $KOBu^t$ resulted in the formation of a mixture of *syn*- and *anti*-oxime derivatives **25** (δ 13.19 and 8.80 ppm, respectively, for the oxime OH ^1H peaks). The ratio of these two isomers was dependent upon the amount of base used. If the reaction was quenched with acetic acid at −78 °C, the formation of syn isomer was favored by 5:1. In contrast, when a large excess (6 mol equiv) of the base was used and the reaction mixture was allowed to warm to room temperature over 1 h, the anti isomer was predominant (2:1 and 88% combined yield). This ratio favoring formation of the anti isomer of **25** could not be improved. However, the isolated syn isomer could be equilibrated to a 2:1 anti/syn mixture under photochemical conditions in MeOH (rt, 1 h), providng the desired anti isomer in 75%

(12) (a) Takai, K.; Hotta, Y.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1978**, 2417−2420. (b) Takai, K.; Hotta, Y.; Oshima, K.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1698−1702. (c) Lombardo, L. *Tetrahedron Lett.* **1982**, *23*, 4293−4296. See also: (d) Lombardo, L. *Organic Syntheses*; Wiley: New York, 1993; Collect. Vol. 8, pp 386−390.

(13) Oppolzer, W.; Bedoya-Zurita, M.; Switzer, C. Y. *Tetrahedron Lett.* **1988**, *29*, 6433−6436.

(14) Review: Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 35−52.

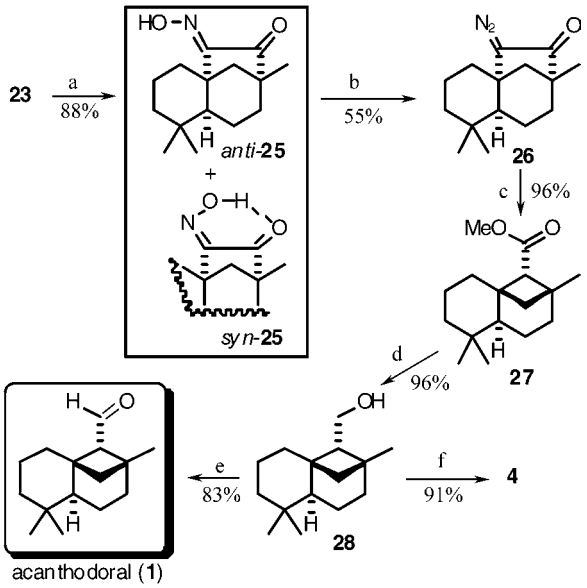
(15) For another example of a palladium-ene reaction that produces an endocyclic alkene product, see: Zair, T.; Santellirouvier, C.; Santelli, M. *Tetrahedron* **1993**, *49*, 3313−3324.

(16) Schadt, F. L.; v. R. Schleyer, P.; Bentley, T. W. *Tetrahedron Lett.* **1974**, 2335−2338.

(17) (a) Danheiser, R. L.; Morin, J. M.; Yu, M.; Basak, A. *Tetrahedron Lett.* **1981**, *22*, 4205−4208. (b) Banwell, M. G.; Harvey, J. E.; Hockless, D. C. R.; Wu, A. W. *J. Org. Chem.* **2000**, *65*, 4241−4250.

(18) Olah, G. A.; Mo, Y. K. In *Carbonium Ions*; Olah, G. A., v. R. Schleyer, P., Eds.; Wiley-Interscience: New York, 1976; Vol. 5, pp 2135−2262.

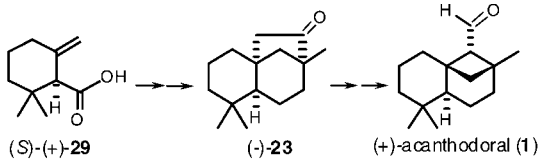
Scheme 4. Synthesis of Acanthodoral (**1**)[a]



[a] Reagents and conditions: (a) *t*-BuOK (6 mol equiv), isoamyl nitrite (1.5 mol equiv), 1 h at −78 °C, then 0.5 h at room temperature; (b) NaOCl (excess), NH_4OH, 0 °C; (c) MeOH, *hν*, rt, 2 h; (d) $LiAlH_4$ (1.6 mol equiv), Et_2O, rt, 2 h; (e) Dess−Martin periodinane (1.2 mol equiv)/CH_2Cl_2, rt, 0.5 h; (f) 4-bromophenyl isocyanate (4 mol equiv)/CCl_4, 60 °C, 2 h.

overall yield from **23** after one recycle. Unexpectedly, only the *anti*-oxime **25** could be converted into α-diazoketone **26** under the Foster conditions.[19] Of the two mechanisms suggested for the Forster reaction,[19b] the one involving attack of NH_2Cl by the lone-pair electrons of the oxime N appears to explain the observed result. Namely, the severe steric conjestion surrounding the oxime N in the syn isomer **25** might not allow a nucleophilic reaction that involves the oxime N lone pair to take place.

Scheme 5. Synthesis of (+)-Acanthodoral (**1**)



Irradiation of diazoketone **26** with UV light in dry MeOH at room temperature cleanly induced a Wolff rearrangement to provide the ring-contracted bycyclo[3.1.1]heptane system **27** (Scheme 4) with the *endo*-methoxycarbonyl group as a single stereoisomer. The endo stereochemistry of the ester was assigned on the basis of a lack of W-type coupling of the ^{1}H NMR peak (δ 2.22 ppm) of the H α to the ester C═O.[20] Ester **27** was then converted to acanthodoral (**1**) in two steps in 80% overall yield. The NMR spectral data of the synthetic alcohol **28** (^{1}H and ^{13}C) and its 4-bromophenyl urethane derivative **4** (^{1}H) were in complete agreement with those derived from natural acanthodoral,[2b] thus confirming the first total synthesis of acanthodoral (**1**).

Optically active acanthodoral was synthesized starting from the known (*S*)-(+)-2,2-dimethyl-6-mehylenecyclohexanecarboxylic acd (**29**).[21] Reduction of this readily availble acid, $[\alpha]_D^{23}$ +121 (*c* 0.10, $CHCl_3$), with $LiAlH_4$ afforded homoallylic alcohol, (+)-**11**, $[\alpha]_D^{23}$ +27.8 (*c* 0.29, $CHCl_3$), with >96% optical purity. Alcohol (+)-**11** was converted into (+)-acanthodoral (**1**), $[\alpha]_D^{22}$ +15.2 (*c* 0.23, $CHCl_3$), following the method described above for the synthesis of its racemate. Although no information pertaining to the absolute configuration of acanthodoral has been reported, on the basis of biogenetic considerations (vide ante), natural acanthodoral is likely to have a dextrorotatory optical rotation.

In summary, the first total synthesis of the marine sesquiterpene aldehyde acanthodoral (**1**) has been achieved commencing with 3-methyl-2-cyclohexen-1-one (**9**) in 19 steps in 2.1% overall yield. Construction of the highly strained bicyclo[3.1.1]heptane skeleton was realized by employing a Wolff rearrangment of the corresponding α-diazoketone with the bicyclo[3.2.1]octane system (**26**). The tricyclic ketone **23** was accessed using a unique palladium-mediated ene reaction of allylic carbonate **12** in the presence of CO, solvolytic ring expansion to the decalin, and a nonreductive acyl radical cyclization.

Acknowledgment. We are grateful to Professor R. J. Andersen of the University of British Columbia for providing us with a copy of the NMR spectra of alcohol **28** and urethane **4**. L.Z. thanks the Eli Lilly Company for a 2002−2003 Industrial Predoctoral Fellowship.

Supporting Information Available: Experimental details as well as spectra of all new compounds described. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) (a) Foster, M. O. *J. Chem. Soc.* **1915**, *107*, 260. (b) Meinwald, J.; Gassman, P. G.; Miller, E. G. *J. Am. Chem. Soc.* **1959**, *81*, 4751−4752.
(20) Coates, R. M.; Kang, H.-Y. *J. Org. Chem.* **1987**, *52*, 2065−2074.
(21) Tanimoto, H.; Oritani, T. *Tetrahedron* **1997**, *53*, 3527−3536.