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Total Synthesis of (+)-4,5-Deoxyneodolabelline

David R. Williams* and Richard W. Heidebrecht, Jr.

Contribution from the Department of Chemistry, Indiana University, Bloomington, Indiana 47405

Received August 1, 2002; E-mail: williamd@indiana.edu

Abstract: The first total synthesis of the marine dolabellane diterpene (+)-4,5-deoxyneodolabelline (**1**) has been accomplished. The highly efficient approach is characterized by the convergent assembly of dihydropyrans **2ab** and cyclopentylsilanes **3ab**. Allylic silane **3a** was prepared from 2-methyl-2-cyclopentenone via a copper-catalyzed 1,4-addition followed by diastereoselective alkylation of the resulting enolate. A chemical resolution of racemic cyclopentanone **8** was effected by (*S*)-CBS-catalyzed borohydride reduction. Direct hydroxymethylation of the enantioenriched ketone **8** to form allylic alcohol **14** was achieved by a Stille palladium-catalyzed cross-coupling from the cyclopentenyl triflate **13**. Treatment of the corresponding allylic phosphate **15** with trimethylsilylcopper reagent provided for displacement with allylic transposition yielding the exocyclic allylsilane **3a** with excellent diastereoselectivity. Dihydropyrans **2a** and **2b** were prepared from optically pure acyclic acetals via ring-closing metathesis. Coupling of **3a** and **2a** or **2b** via the carbon-Ferrier protocol gave *trans*-2,6-disubstituted dihydropyrans **30** and **35** with complete stereoselectivity. Vanadium-based pinacol coupling reactions were explored for closure of the medium-sized carbocycle to yield *syn*-diol **33**. X-ray diffraction studies of the monobenzoate **34** have provided unambiguous stereochemical assignments. Substantial ring strain accounted for the lack of alkene products typical of reductive elimination using $TiCl_3$ and zinc−copper couple (McMurry) conditions leading to **37**. Finally, the natural product **1** was obtained via Swern oxidation of the diol **37**.

Introduction

The dolabellanes are a family of bicyclic diterpenes which were originally discovered as metabolites of the sea hare *Dolabella californica*.[1] Since 1975, more than 140 unique structures have been reported from many sources.[2] Dolabellanes and neodolabellanes share a characteristic bicyclo[9.3.0]-tetradecane skeleton (Figure 1). The biogenesis of dolabellanes is proposed to initiate from a π−cation cyclization of geranylgeranyl pyrophosphate. Neodolabellanes are the products of subsequent stereospecific migrations of hydrogen and methyl substituents along the carbon backbone, which accounts for the stereochemistry at C_{11} and C_{12}, and the translocation of the methyl substituent (C15) across the ring fusion in these metabolites as compared to the parent skeleton.

It was originally believed that these diterpenes were exclusively of marine origin. However, several terrestrial sources have been discovered.[2a,b] Earlier studies had proposed that the widespread occurrence of dolabellanes in the marine ecosystem was a result of dietary intake, distribution, and further metabolism.[3] While this may be true in many cases, it is now recognized that related structures from different species have opposite absolute stereochemistry, suggesting phenomena of bioconvergence.[2]

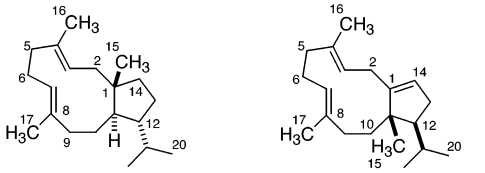

Figure 1.

The dolabellanes have exhibited an impressive range of biological properties, including significant cytotoxic, antibacterial, and antiviral activity.[4] Reports include effective inhibition of K^+-induced contractions in blood aortic strips, while another notes blockage of Ca^{2+} channels in isolated smooth muscle tissue.[5] Dolabellanes can also display ichthyotoxic and phytotoxic properties,[6] and the recent discovery of novel structures continues to spur interest in the family.[7] Moreover, the 3,7-dolabelladienes serve as direct biogenic precursors of the 5−7−6 tricyclic terpenes of the dolastane class, many of which display significant antitumor properties.[8]

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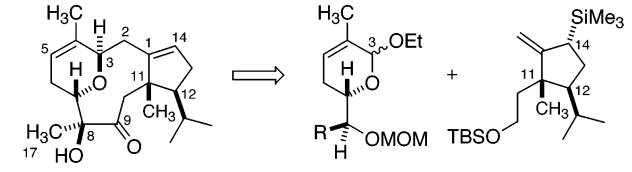
(2) (a) For a review: Rodriguez, A. D.; Gonzalez, E.; Ramirez, C. *Tetrahedron* **1998**, *54*, 11683. (b) Asakawa, Y.; Lin, X.; Tori, M.; Kondo, K. *Phytochemistry* **1990**, *29*, 2597.
(3) (a) Sun, H. H.; Fenical, W. *Phytochemistry* **1979**, *18*, 340. (b) Ireland, C.; Faulkner, D. J. *J. Org. Chem.* **1977**, *42*, 3157.
(4) (a) Mori, K.; Iguchi, K.; Yamada, N.; Yamada, Y.; Inouye, Y. *Chem. Pharm. Bull.* **1988**, *36*, 2840. (b) Tringali, C.; Piattelli, M.; Nicolosi, G. *Tetrahedron* **1984**, *40*, 799.
(5) (a) Su, J.; Zhong, Y.; Shi, K.; Cheng, Q.; Synder, J. K.; Hu, S.; Huang, T. *J. Org. Chem.* **1991**, *56*, 2337. (b) Su, J.; Zong, Y.; Zeng, L.; *J. Nat. Prod.* **1991**, *54*, 380.
(6) Van Onckelen, H. A.; Verbeek, R. *Phytochemistry* **1972**, *11*, 1677.
(7) For recent isolation papers: (a) Duh, C.-Y.; Chia, M.-C.; Wang, S.-K.; Chen, H.-J.; El-Gamal, A. A. H.; Dai, C.-H. *J. Nat. Prod.* **2001**, *64*, 1028. (b) Hinkley, S. F.; Mazzola, E. P.; Fettinger, J. C.; Lam, Y.-F.; Jarvis, B. B. *Phytochemistry* **2000**, *55*, 663. (c) Costantino, V.; Fattorusso, E.; Mangoni, A.; Di Rosa, M.; Ianaro, A.; Aknin, M.; Gaydou, E. M. *Eur. J. Org. Chem.* **1999**, *1*, 227.

Scheme 1

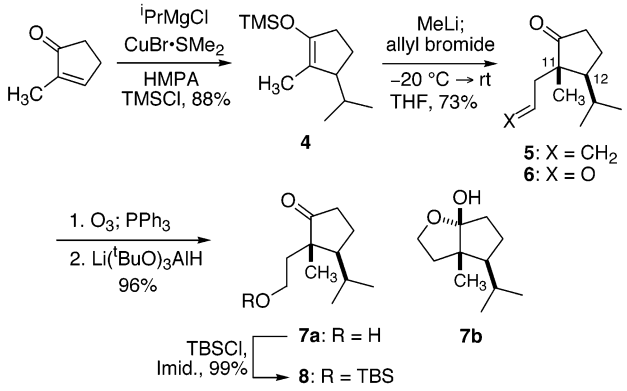


Several investigations have focused on strategies for construction of these eleven-membered macrocyclic structures. In 1993, we reported the first synthesis of fully elaborated dolabellanes via intramolecular Julia reactions of α-sulfonyl carbanions,[9a] and in 1995, we described the first synthesis of α- and *β*-neodolabellenol.[9b] An intramolecular alkylation route was also reported in 1993, leading to a dolabellane progenitor for biomimetic transannular cyclization resulting in the total synthesis of (−)-3α,4*β*-dihydroxyclavulara-1(15),17-diene, an example of the dolastane family.[10] Jenny and Borschberg demonstrated ring closure via an enolate alkylation to provide for synthesis of the hydrocarbon (±)-*δ*-araneosene,[11] while Yamada and co-workers have also utilized an intramolecular alkylation strategy for the synthesis of claenone.[12]

Rearrangements leading to both ring expansions and ring contractions have been effective processes for development of the eleven-membered carbocycles. Mehta published an early study of the oxy-Cope ring expansion reaction toward the dolabellanes.[13] Subsequently, Corey and Kania described a noteworthy enantioselective Claisen rearrangement, as well as the anionic oxy-Cope reaction for the synthesis of these diterpenes.[14]

Recent investigations in our laboratories have pursued strategies for the efficient assembly of cyclic diterpenes which contain bridging ether linkages. Many marine terpenes incorporate five- and six-membered ethers as a consequence of transannular cyclization events. In this regard, 4,5-deoxyneodolabelline (**1**), a metabolite of an Australian soft coral, is a typical example (Scheme 1).[15] The parent compound, neodolabelline, was first identified as the 4,5-epoxide of **1**, and structural elucidation was completed by X-ray diffraction of the C1/C14 dibromide derivative.[16] Deoxygenation of neodolabelline with Zn(Cu) in refluxing ethanol gave the olefin **1** (55%), thereby establishing the structural and stereochemical relationship of these metabolites.

Scheme 2



A convergent plan for total synthesis of **1** is suggested via bond disconnections at C_2/C_3 and at C_8/C_9 to provide precursors **2** and **3**. Each component contains approximately one-half of the structural information and the molecular complexity of the natural product (**1**), providing an attractive element of simplicity for the overall scheme.

Results and Discussion

Our studies initially focused on a convenient pathway for preparation of the cyclopentenyl silane **3**. Using a four-step procedure, which had been developed and optimized in our previous efforts,[9a] the copper-catalyzed conjugate addition of isopropylmagnesium chloride with 2-methyl-2-cyclopentenone was accelerated in the presence of trimethylsilyl chloride.[17] Piers and Renaud reported similar findings,[18] and the presence of hexamethylphosphoric triamide as a necessary additive resulted in high yields of the silyl enol ether **4** (Scheme 2). Treatment of **4** with methyllithium at −20 °C facilitated regiocontrolled access to the tetrasubstituted enolate which underwent stereoselective alkylation with allyl bromide.

Ozonolysis of **5** followed by immediate reduction of aldehyde **6** with lithium tri-*tert*-butoxyaluminohydride selectively provided alcohol **7a** and hemiketal **7b** as an equilibrating mixture (2.4:1 ratio in $CDCl_3$ solution). Treatment of this mixture with *tert*-butyldimethylsilyl chloride (TBSCl) and imidazole at room temperature led to nearly quantitative yields of the desired ketone **8**. The attractive sequence was favored because it readily permitted the dependable preparation of 50-g quantities of **8** in 61% overall yield, although it clearly suffered from a lack of enantiocontrol. While the latter objective was also feasible beginning from a chiral pool precursor, the process required many more steps with lower efficiency.

Chemical resolution of **8** was accomplished by asymmetric reduction utilizing the Corey CBS borohydride reaction.[19] The slow addition of cyclopentanone **8** into a warm solution of oxazaborolidine catalyst and borane dimethyl sulfide complex at 40 °C was necessary to obtain products with satisfactory

(8) Dolatriol was the first example: Pettit, G. R.; Ode, R. H.; Herald, C. L.; Von Dreele, R. B.; Michel, C. *J. Am. Chem. Soc.* **1976**, *98*, 4677. Recently, representatives of this class, known as trichoaurantianolides and guanacastepenes, have been isolated from fungi, and display the methyl migration characterizing the neodolabellanes, as well as the 5−7−6 tricyclic skeleton of the dolastanes. Benevelli, F.; Carugo, O.; Invernizzi, A. G.; Vidari, G. *Tetrahedron Lett.* **1995**, *36*, 3035. Brady, S. F.; Bondi, S. M.; Clardy, J. *J. Am. Chem. Soc.* **2001**, *123*, 9900. For a recent report on the total synthesis of guanacastepene A: Lin, S.; Dudley, G. B.; Tan, D. S.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 2188.

(9) (a) Williams, D. R.; Coleman, P. J.; Nevill, C. R.; Robinson, L. A. *Tetrahedron Lett.* **1993**, *34*, 7895. (b) Williams, D. R.; Coleman, P. J. *Tetrahedron Lett.* **1995**, *36*, 35.

(10) Williams, D. R.; Coleman, P. J. *Tetrahedron Lett.* **1995**, *36*, 39.

(11) (a) Jenny, L.; Borshberg, H.-J. *Helv. Chim. Acta* **1995**, *78*, 715. (b) For a recent palladium-mediated approach: Hu, T.; Corey, E. J. *Org. Lett.* **2002**, *4*, 2441.

(12) (a) Miyaoka, H.; Isaji, Y.; Kajiwara, Y.; Kunimune, I.; Yamada, Y. *Tetrahedron Lett.* **1998**, *39*, 6503. (b) See also: Kato, N.; Higo, A.; Wu, X.; Takeshita, H. *Heterocycles* **1997**, *46*, 123.

(13) Mehta, G.; Karra, S. R.; Krishnamurthy, N. *Tetrahedron Lett.* **1994**, *35*, 2761.

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(15) Bowden, B. F.; Coll, J. C.; Gulbis, J. M.; Mackay, M. F.; Willis, R. H. *Aust. J. Chem.* **1986**, *39*, 803.

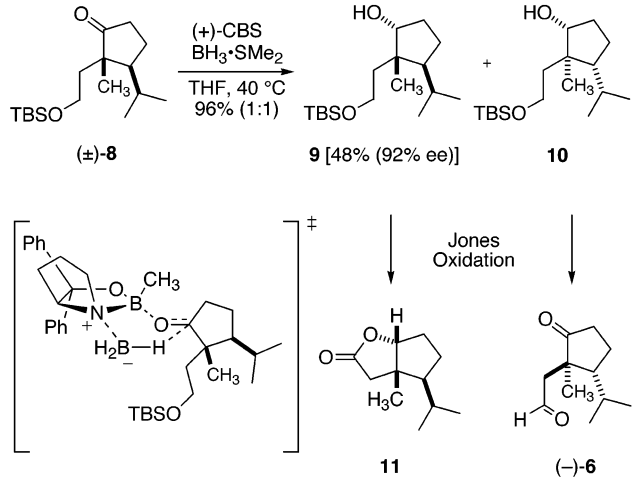
(16) Kobayashi, M.; Son, B.-W.; Fujiwara, T.; Kyogoku, Y.; Kitagawa, I. *Tetrahedron Lett.* **1984**, *25*, 5543.

(17) For information regarding TMSCl and organocopper reagents: Nakamura, E. Me_3SiCl-accelerated conjugate addition reactions of organocopper reagents. In *Organocopper Reagents*; Taylor, R. J. K., Ed.; Oxford University Press: New York, 1994; pp 129−140.

(18) Piers, E.; Renaud, J. *J. Org. Chem.* **1993**, *58*, 11.

(19) For a general review: Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986.

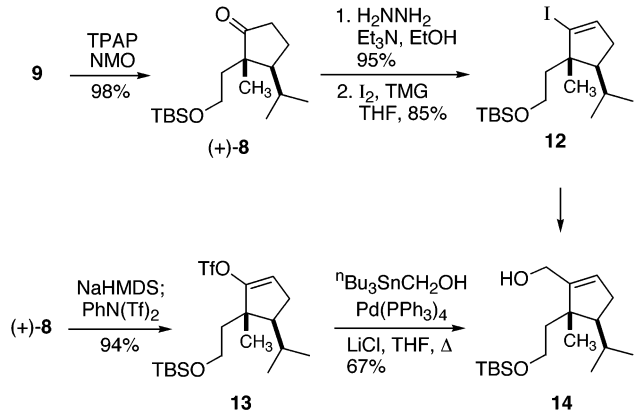
Scheme 3



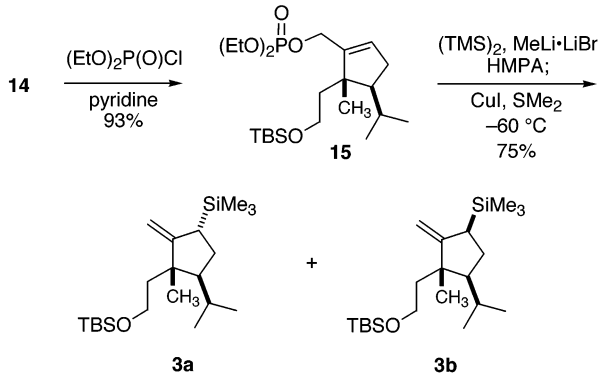
optical purity.[20,21] Equal quantities of two diastereomeric cyclopentanols **9** and **10** were readily separated by flash silica gel chromatography. Product formation can be rationalized as illustrated in Scheme 3 via an internally directed hydride addition to the activated ketone **8** through diastereomeric transition states which place the bulky α-position toward the convex face of the cis-fused CBS scaffold. Thus, facial selectivity is not influenced by the absolute stereochemistry of the fully substituted α-carbon of **8**. Assignments of relative stereochemistry for **9** and **10** were confirmed, following the treatment of the individual alcohols with Jones' reagent at −10 °C (THF; Celite), yielding the cis-fused lactone **11** and the keto aldehyde (−)-**6**, respectively.[22]

Our synthesis plan required the transformation of ketone **8** into an allylic system with the addition of a methylene unit. Upon TPAP oxidation[23] of the optically enriched cyclopentanol **9**, two options were explored for one-carbon homologation of the (+)-cyclopentanone **8** (Scheme 4). Initial formation of the hydrazone derivative permitted a radical-induced decomposition leading to the cyclopentenyl iodide **12** with loss of nitrogen in the presence of 1,1,3,3-tetramethylguanidine (TMG).[24] While the low-temperature halogen−metal exchange of **12** was effective, the preparative-scale alkylations with gaseous formaldehyde leading to **14** proceeded with significantly reduced yields.[25] A palladium-catalyzed cross-coupling strategy proved most successful for conversion of the ketone **8** to the requisite allylic

Scheme 4



Scheme 5



alcohol **14**. Transformation of **8** to the corresponding triflate **13** was followed by Stille cross-coupling[26] with tri-*n*-butylstannylmethanol (Scheme 4)[27,28] Initial attempts noted that consumption of stannane was much faster than that of the triflate. Thus, syringe-pump addition of tri-*n*-butylstannylmethanol to the reaction mixture, maintained at 70 °C, afforded the allylic alcohol in 67% yield. Examination of the catalyst load revealed that 5% $(Ph_3P)_4Pd$ with 3 equiv of LiCl (based on triflate) afforded highly reproducible reactions, however, the allylic alcohol **14** was invariably accompanied by protodesulfonated cyclopentene. This reduction pathway has been recognized as the result of butyl group participation from the Pd-insertion intermediate resulting in *β*-hydride elimination. The procedure has been used to reduce triflates to their corresponding alkenes.[29] In our case, this complication could reasonably be circumvented by the use of the analogous trimethylstannyl methanol but was not explored in favor of the use of the less volatile tri-*n*-butylstannane.

Esterification of alcohol **14** was followed by S_N2' displacement of the diethyl phosphate by trimethylsilyl cuprate (Scheme 5).[30] Exclusive formation of the exo olefin was observed, and the allylsilane **3** was formed as a 24:1 ratio of **3a**:**3b** diastereomers. We observed a progressive erosion of diastereoselectivity

(20) (a) For temperature effects on CBS reduction: Stone, G. B. *Tetrahedron: Asymmetry* **1994**, *5*, 465. (b) For a related reduction of an α,α-disubstituted cyclopentanone: Denmark, S. E.; Schnute, M. E.; Marcin, L. R.; Thorarensen, A. *J. Org. Chem.* **1995**, *60*, 3205.

(21) (a) The optical purities were determined by Mosher ester analysis: Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2534. (b) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1973**, *95*, 512. (c) The esters were prepared using a carbodiimide coupling: Albert, J. S.; Hamilton, A. D. 1,3-Dicyclohexylcarbodiimide-4-Dimethylaminopyridine. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; John Wiley and Sons: Chichester, England, 1995; Vol. 3, pp 1755−1756.

(22) The lactone **11** was also confirmed via the unambiguous stepwise elaboration from **9** by acetylation of the secondary alcohol, TBS ether cleavage, TPAP oxidation, deacetylation with methanolic potassium carbonate, and TPAP oxidation of the resulting lactol. Keto aldehyde (−)-**6** was compared to racemic material from direct oxidative cleavage of (±)-**5**.

(23) (a) Griffith, W. P.; Ley, S. V.; Whitcombe, G. P.; White, A. D. *J. Chem. Soc., Chem. Commun.* **1987**, 1625. (b) Griffith, W. P.; Ley, S. V. *Aldrichimica Acta* **1990**, *23*, 13.

(24) (a) Barton, D. H. R.; Bashiardes, G.; Fourrey, J. L. *Tetrahedron Lett.* **1983**, *24*, 1605. (b) Coleman, P. J. Ph.D. Thesis, Indiana University, August 1994.

(25) Transformation to **14** was also carried out in moderate overall yield by halogen/lithium exchange of **12** (^{n}BuLi/Et_2O/-78 °C), acylation with methyl chloroformate, and hydride reduction.

(26) Scott, W. J.; Stille, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 3033.

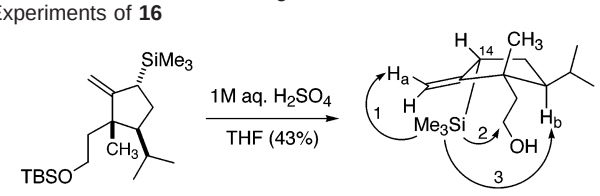
(27) For preparation of the stannane: Danheiser, R. L.; Romines, K. R.; Koyama, H.; Gee, S. K.; Johnson, C. R.; Medich, J. R. *Org. Synth.* **1993**, *71*, 133.

(28) (a) For previous results utilizing this unprotected stannane: Kosugi, M.; Sumiya, Y.; Ohhashi, K.; Sano, H.; Migita, T. *Chemistry Lett.* **1985**, 997. (b) Yasuda, N.; Yang, C.; Wells, K. M.; Jensen, M. S.; Hughes, D. L. *Tetrahedron Lett.* **1999**, *40*, 427.

(29) Cook, G. K.; Hornback, W. J.; Jordan, C. L.; McDonald, J. H., III; Monroe, J. E. *J. Org. Chem.* **1989**, *54*, 5828.

(30) Smith, J. C.; Henke, S. L.; Mohler, E. M.; Morgan, L.; Rajan, N. I. *Synth. Comm.* **1991**, *21*, 1999.

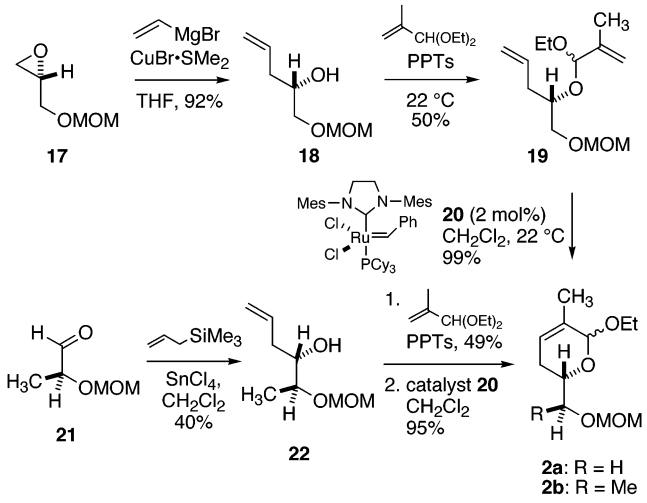
Table 1. Stereochemical Assignment of **3a** via nOe NMR Experiments of **16**



3a **16**

entry	irradiation	% nOe
1	Me_3Si	4.4% H_a
2	Me_3Si	1.3% CH_2
3	Me_3Si	3.4% H_b

Scheme 6

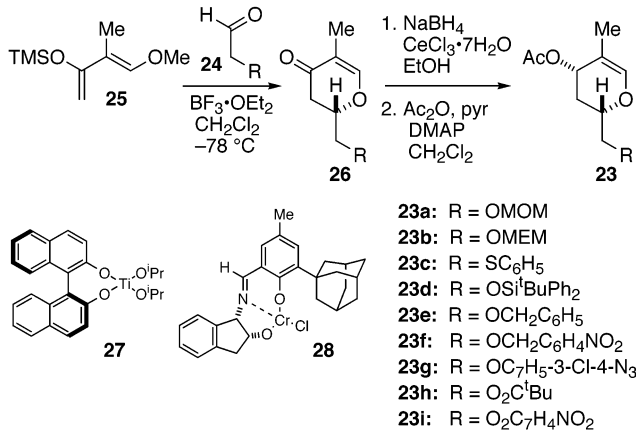


as the scale of the reaction was increased from approximately 100 mg of **15** to the 2-g level. This was attributed to the prolonged cannulation of the cuprate and local exotherms in the larger-scale reactions. Fortunately, our subsequent experiments demonstrated that either diastereomer **3a** or **3b** could be effectively utilized without stereochemical consequences (vide infra). The stereochemical selectivity of the allylic displacement can be rationalized by the preferred pseudoaxial addition of the silyl reagent with the cyclopentenyl conformer characterized by pseudoequatorial disposition of the isopropyl group.

Careful silica gel chromatography led to the isolation of pure samples of **3a** for complete characterization. The relative stereochemistry at C_{14} of **3a** was secured via nOe difference experiments after silyl ether hydrolysis as shown in Table 1.[31]

Synthesis of the 5,6-Dihydropyran Component. Syntheses of homochiral dihydropyrans **2a** and **2b** were accomplished using two pathways which differed in the nature of the substitution at C_8 (Scheme 6). The C-8 desmethyl-5,6-dihydropyran **2a** was prepared in four steps. Protection of (*R*)-glycidol as its methoxymethyl ether **17**[32] was followed by copper-catalyzed nucleophilic oxirane opening using vinylmagnesium bromide. Formation of the mixed acetal **19** was promoted by acid-catalyzed exchange of ethanol at room temperature under reduced pressure (55 mmHg).[33]

Scheme 7



Finally, ring-closing metathesis using the Grubbs ruthenium catalyst **20**, bearing the 1,3-dimesityl-4,5-dihydroimidazole-2-ylide ligand, provided the desired **2a** as a 1:1 mixture of anomers.[34] The metathesis reaction is a superior strategy for synthesis of these dihydropyrans.[35] In our example, catalyst loads as low as 2% were utilized to effect cyclization at room temperature in nearly quantitative yields. By comparison, experiments using the bis-tricyclohexylphosphine-based ruthenium catalyst[36] also provided **2a**, although reactions failed to progress to completion even with high catalyst loads.

A second pathway was developed to incorporate the C-8 methyl substituent. The known aldehyde **21**[37] was transformed into the homoallylic alcohol **22** via the chelation-controlled addition[38] of allyltrimethylsilane at −78 °C. As anticipated, acetal exchange and ring-closing metathesis yielded **2b** (95%) as a mixture (1:1) of ethyl acetals.

Formation of the C_2-C_3 Bond via Allylation. Fundamental understanding of our proposed allylation process requires some digression of the discussion to describe our initial plans for a convergent synthesis involving the use of a carbon-Ferrier strategy as precedented, in principle, by the elegant work of Danishefsky, Fraser-Reid, and others.[39,40] To this end, we prepared the glycals **23** as shown in Scheme 7. Substituted acetaldehydes **24** were subjected to hetero-Diels−Alder reactions with diene **25**[41] using boron trifluoride etherate at −78 °C. The racemic γ-pyranones **26** were isolated in approximately 50−60% yields, and a subsequent Luche reduction[42] was followed by acetylation to provide the equatorial acetates **23**.

(31) For a similar deprotection: Trost, B. M.; Grese, T. A.; Chan, D. M. T. *J. Am. Chem. Soc.* **1991**, *113*, 7350.
(32) Bachki, A.; Foubelo, F.; Yus, M. *Tetrahedron: Asymmetry* **1995**, *6*, 1907.
(33) (a) Mulzer, J.; Hanbauer, M. *Tetrahedron Lett.* **2000**, *41*, 33. (b) Crimmins, M. T.; King, B. W. *J. Am. Chem. Soc.* **1998**, *120*, 9084.
(34) (a) Grubbs, R. H.; Miller, S. J.; Fu, G. C. *Acc. Chem. Res.* **1995**, *28*, 446. (b) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (c) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953.
(35) (a) Rutjes, F. P. J. T.; Kooistra, T. M.; Hiemstra, H.; Schoemaker, H. E. *Synth. Lett.* **1998**, 192. (b) Weatherhead, G. S.; Houser, J. H.; Ford, J. G.; Jamieson, J. Y.; Schrock, R. R.; Hoveyda, A. H. *Tetrahedron Lett.* **2000**, *41*, 9553. (c) Nadolski, G. T.; Davidson, B. S. *Tetrahedron Lett.* **2001**, *42*, 797. (d) Enev, V. S.; Kaehlig, H.; Mulzer, J. *J. Am. Chem. Soc.* **2001**, *123*, 10764.
(36) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18−29.
(37) Aldehyde **21** was synthesized from (*S*)-ethyl lactate in three steps: Banfi, L.; Bernardi, A.; Colombo, L.; Gennari, C.; Scolastico, C. *J. Org. Chem.* **1984**, *49*, 3784.
(38) (a) Heathcock, C. H.; Kiyooka, S.; Blumenkopf, T. A. *J. Org. Chem.* **1984**, *49*, 4214. (b) The antipode of **22a** is known: Brabander, J. D.; Vandewalle, M. *Synthesis* **1994**, 855.
(39) (a) Ferrier, J. R. *J. Chem. Soc.* **1964,** 5443. (b) Ferrier, J. R.; Prasad, N. *J. Chem. Soc. (C)* **1969**, 570. (c) Hurd, C. D.; Bonner, W. A. *J. Am. Chem. Soc.* **1945**, *67*, 1664. (d) Danishefsky, S.; Kerwin, J. F. *J. Org. Chem.* **1982**, *47*, 3805.
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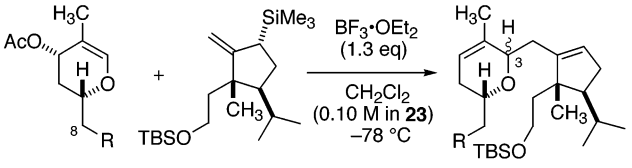
(41) (a) Clive, D. L.; Berstra, R. J. *J. Org. Chem.* **1991**, *56*, 4976. (b) Sugasawa, S.; Yamada, S.; Narahashi, M. *J. Pharm. Soc. Jpn.* **1951**, *71*, 1345.

Table 2. Diastereoselection in Allylation Reactions



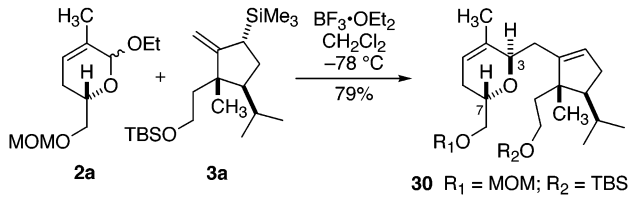
23 (1.0 eq) **3a** (1.2 eq) **29a**: (C_3 α–H) **29b**: (C_3 β–H)

entry	ratio of **29a**/**29b**	yield, %
23a R = OMOM	9:1	99
23b R = OMEM	8.1:1	80
23c R = SC_6H_5	3.5:1	91
23d R = OSi^tBuPh_2	3.5:1	68
23e R = $OCH_2C_6H_5$	1.8:1	91
23f R = $OCH_2C_6H_4NO_2$	4.6:1	97
23g R = OC_7H_5-3-Cl-4-N_3	6.7:1	96
23h R = O_2C^tBu	1.9:1	80
23i R = $O_2C_7H_4NO_2$	2.2:1	54

The silyl ether **26** (R = OSi^{t}BuPh2) was cleaved (TBAF, THF) to give the corresponding primary alcohol **26** (R = OH) which permitted the incorporation of various acid-labile esters and ethers not well tolerated under the hetero-Diels−Alder conditions. Among these alternatives, the methoxymethyl (MOM)-substituted example **23a** demonstrated the most promise in our allylation studies (vide infra). Thus, asymmetric induction was examined for Diels−Alder cycloadditions of acetaldehyde **24** (R = OMOM). Use of the 1,1′-bi-2-naphthol (BINOL)-based titanium catalyst **27** as developed by Keck[43] led to a 37% yield of **26** (R = OMOM) with 84% ee.[44] Similar explorations of the salen-based chromium catalyst **28** described by Jacobsen[45] improved the yield of the hetero-Diels−Alder product **26** (R = OMOM) (87%), but resulted in a deterioration of optical purity.[46]

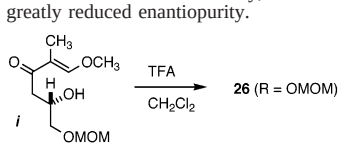
Unforeseen problems also became apparent in the course of subsequent studies of the allylation-Ferrier process. Upon attempted optimization of our glycal reactions with pure allylsilane **3a** (Table 2) using boron trifluoride etherate at −78 °C, we observed that diastereoselectivity was strongly affected by the nature of the remote protecting group (at C_8) in **23**. Product ratios of major isomer, 2,6-*trans*-disubstituted 3,6-dihydro-2H-pyrans **29a**, and the *cis*-2,6-disubstituted (minor) **29b** were determined by the integration of pairs of NMR signals for the C_3 hydrogens, which were not further complicated by the chirality (at C_{11} and C_{12}) of the cyclopentene.[47] The choice of methoxymethyl (MOM) or β-methoxyethoxymethyl (MEM) ethers **23a** or **23b** provided for the most stereoselective allylations as summarized in Table 2. The thiophenyl example **23c**, the *tert*-butyldiphenyl silyl (TBDPS) ether **23d**, and the electron-deficient benzyl ethers **23f** and **23g** led to modest selectivity. However, the use of simple esters, as typified by the pivaloate **23g** and the *p*-nitrobenzoate **23i**, as well as that of the benzyl ether **23e** gave surprisingly inferior results.[48] Stronger Lewis acids also generally resulted in a deterioration of diastereoselectivity.[49]

The aforementioned problems of the glycal pathway led to the development of the olefin metathesis route of Scheme 6 as a source of electrophilic coupling partners for our allylations. In the event, reaction of optically active dihydropyran acetal **2a** and allylsilane **3a** afforded a single diastereoisomer **30**. A survey of Lewis acids demonstrated that $BF_3{\cdot}OEt_2$ was optimum. Since a slight excess of acetal **2a** (1.3:1 ratio of **2a** to **3a**) proved to be beneficial, unconsumed dihydropyran was recovered and was observed to be predominantly one diastereomer (>95:5). The same dihydropyran anomer was also generated by thermodynamic equilibration of the 1:1 mixture of acetals **2a** under mildly acidic conditions with PPTs in ethanol (22 °C) or with $BF_3{\cdot}OEt_2$ (CH_2Cl_2 at −78 °C). This pseudoaxial α-anomer[50] was coupled with silane **3a** to provide **30** in the same yields as were previously observed with the mixture **2a**, thus establishing that both anomers of the starting acetal were equally reaction-competent via a common oxocarbenium ion or initial acetal isomerization. Additionally, we briefly examined the role of the protecting group at C-8. Synthesis of the analogous *tert*-butyldimethylsilyl (TBS) ether of **2a** was achieved via the pathway described in Scheme 6. In contrast to our previous efforts in Table 2, allylations using the corresponding TBS ether of **2a** proceeded to give the bis-TBS ether **30** (R_1 = R_2 = TBS) in 73% yield with 100% stereoselectivity.



The influence of stereochemistry in the silanes **3ab** was also examined. A control experiment combining a 1:1 mixture of allylsilane diastereomers **3ab** and the usual mixture of acetal anomers **2a** (1:1 ratio) was performed. This reaction provided **30** as a single diastereomer (at C-3) in yields comparable to those previously observed from pure **3a**. A more detailed

(42) (a) Luche, J. L.; Rodriguez-Hahn, L.; Crabbe, P. *Chem. Commun.* **1978**, 601. (b) Gleason, M. M.; McDonald, R. E. *J. Org. Chem.* **1997**, *62*, 6432.
(43) Keck, G. E.; Li, X.-Y.; Krishnamurthy, D. *J. Org. Chem.* **1995**, *60*, 5998.
(44) Remaining material was identified as the Mukaiyama aldol product ***i*** which was cyclized to **26** with mild acid. Unfortunately, these additional quantities of **26** exhibited greatly reduced enantiopurity.



(45) Dossetter, A. G.; Jamison, T. F.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **1999**, *38*, 2398.
(46) These efforts produced **26** in 50−60% ee as determined by subsequent cleavage of the methoxymethyl ether yielding **26** (R = OH), and formation of diastereomers by Mosher esterification analysis.
(47) For many entries of Table 2, the pairs of *trans*-2,6-pyrans **29a** and *cis*-**29b** were separated by flash silica gel chromatography. Confirmation of the structure assignment was provided by comparison with authentic **30** and the subsequent X-ray diffraction study of **34**.
(48) Although the carbon-Ferrier reactions would appear to proceed via a commonly held oxocarbenium species, a clear pattern of reactivity emerged from our experiments with a series of C_8 benzyl ethers. Electron-donating substituents, such as the *p*-methoxy benzyl ether (PMB) led to a highly reactive glycal **23** and poor allylation results, whereas one or more electron-withdrawing aryl substituents (nitro, chloride, and azido substituents were examined without optimization) provided for sequentially improved yields and diastereoselectivity for **29**.
(49) The reactivity of the nucleophilic olefin may also be an important factor. Trials with less reactive allyltrimethylsilane and **23** generally resulted in higher selectivity. Related studies using silyl ketene acetals report modest diastereoselectivity. See: Paterson, I.; Smith, J. D.; Ward, R. A. *Tetrahedron* **1995**, *51*, 9413.
(50) The stereochemistry of the thermodynamically more stable acetal is assumed on the basis of comparisons with closely related dihydropyran systems. See: Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon Press: New York, 1983; pp 4−21.

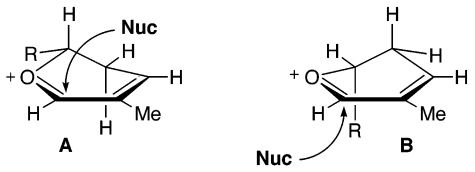


Figure 2. Stereocontrolled nucleophilic attack for conformers **A** and **B**.

analysis was also performed by running reactions to 50% completion by a reduction in the quantity of Lewis acid. Unconsumed silane showed an enrichment of the β-isomer **3b** (recovery ratio **3a**:**3b** was 2.2:1). On the basis of the knowledge of the starting ratio of **3ab** (3.3:1), concentrations [**3a**] and [**3b**] of each allylsilane diastereomer at the initiation (t_0) and termination ($t_{1/2}$) of the reaction were determined. The ratio of the rate expressions as shown in eq 1 indicated that the predominant **3a** reacted approximately twice as fast as **3b**. The slight differences in reactivity of our diastereomers **3ab** are more interesting in a mechanistic context. However, the impressive diastereoconvergence of our reaction pathway dramatically facilitated a successful synthesis.

$$\text{relative rate of reaction for } \mathbf{3a}/\mathbf{3b} = \frac{k_\alpha}{k_\beta} = \frac{\ln \dfrac{[\mathbf{3a}]t_{1/2}}{[\mathbf{3a}]t_0}}{\ln \dfrac{[\mathbf{3b}]t_{1/2}}{[\mathbf{3b}]t_0}} = 2 \qquad (1)$$

Rationalization of the stereochemical outcome of the coupling process recognizes two conformers of the oxocarbenium intermediate as distinguished by the pseudoequatorial substituent in **A** and the pseudoaxial substituent in **B** (Figure 2). From this standpoint, it is noteworthy that stereoelectronically controlled axial attack of the allylsilane **3ab** with the more stable conformer **A** dominates the reaction coordinate leading to the observed 2,6-*trans*-dihydropyran **30** via a developing chair transition state.

The similar rates of reactions for **3a** and **3b** provide additional mechanistic insights. The addition reactions of allylsilanes and aldehydes are commonly rationalized by open transition states as described by synclinal and anticlinal arrangements.[51] A dominant feature of these transition states is the anti orientation of the carbon−silicon bond with the newly forming carbon−carbon bond. This factor provides for electron donation stabilizing the transition state. Further considerations of the diastereomeric relationship of **3a** and **3b** suggest that the major isomer **3a** proceeds via the synclinal arrangement, whereas **3b** reacts similarly via the anticlinal situation (Figure 3). Steric interactions are significant factors controlling the relative ease of these reactions, and these effects are minimized, to an equal extent, with respect to the adjacent quaternary carbon of the silane diastereomers, as illustrated below. On the other hand, the consistent application of either the synclinal or anticlinal model to both diastereomers would lead to problematic concerns stemming from steric interactions with substituents of the quaternary carbon, and certainly portend differences in the effectiveness and rates of these allylations.

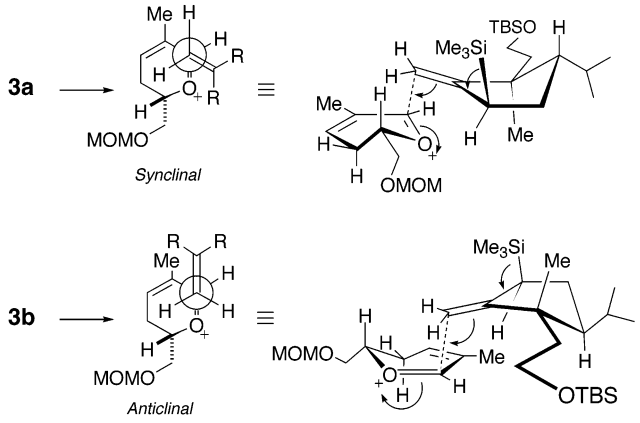
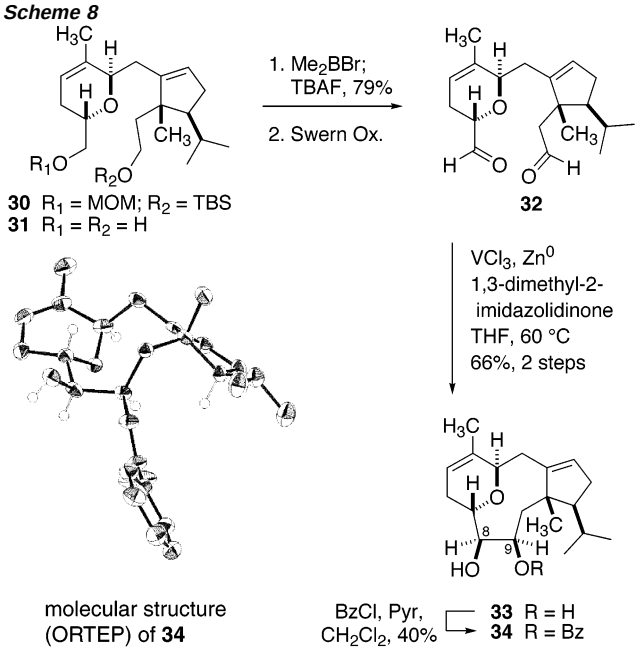


Figure 3. Synclinal and anticlinal arrangements as shown from Newman projections and 3-D representations.

Scheme 8



Reductive Coupling for Nine-Membered Ring Formation. Construction of the neodolabelline ring system required C_8−C_9 bond formation beginning with the protected diol **30**. The limited degrees of freedom imposed by the preexisting rings in **30** were viewed as a positive contributor for effective closure of the nine-membered ring via a reductive coupling strategy. Aside from issues of stereochemistry, a caveat of this approach was the potential for reductive elimination that would open the dihydropyran ring. As shown in Scheme 8, sequential deprotections of **30** gave diol **31** by removal of the MOM[52] and silyl ethers, respectively. Swern oxidation[53] led to the labile dialdehyde **32**, and reductive coupling using $[V_2Cl_3(THF)_6]_2[ZnCl_6]$[54] gave the diol **33** as the major component of a 9:1 mixture of diastereomers (66% for two steps). Preferential production of *cis*-diols is attributed to vanadium chelation in this pinacol

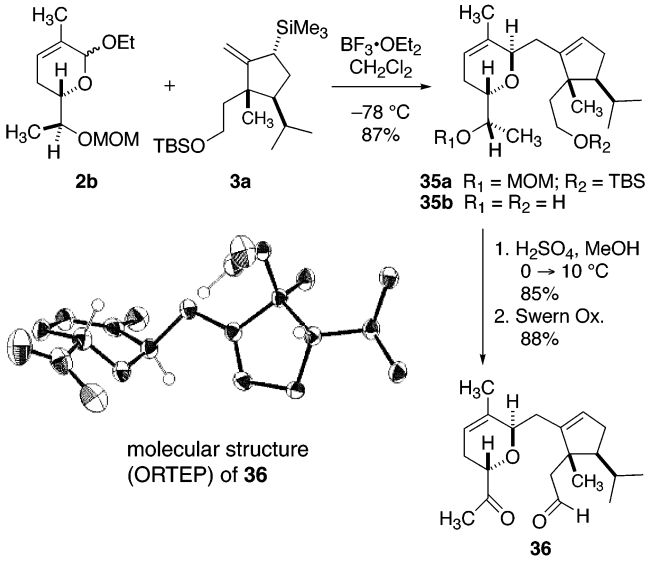
(51) Calculations indicate similar opportunities for synclinal and anticlinal transition states: Paddon-Row: M. N.; Rondan, N. G.; Houk, K. N. *J. Am. Chem. Soc.* **1982**, *104*, 7162. Some examples include: Denmark, S. E.; Weber, E. J. *Helv. Chim. Acta* **1983**, *66*, 1655. Danishefsky, S. J.; DeNinno, S.; Lartey, P. *J. Am. Chem. Soc.* **1987**, *109*, 2082. Masse, C. E.; Panek, J. S. *Chem. Rev.* **1995**, *95*, 1293. Fleming, I.; Dunogues, J.; Smithers, R. *Org. React.* **1989**, *37*, 57.

(52) (a) Guidon, Y.; Morton, H. E.; Yoakim, C. *Tetrahedron Lett.* **1983**, *24*, 3969. (b) Guidon, Y.; Yoakim, C.; Morton, H. E. *J. Org. Chem.* **1984**, *49*, 3912.

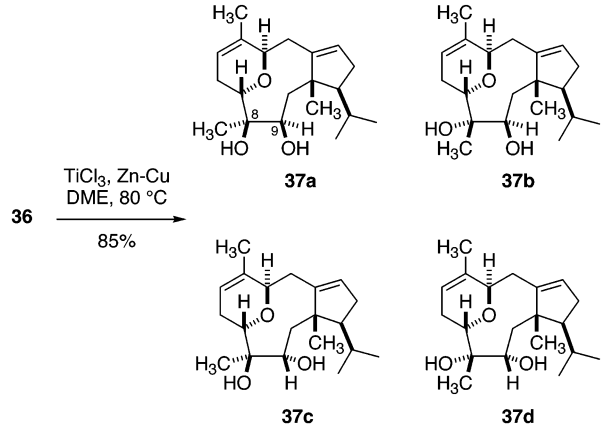
(53) Mancuso, A. J.; Huang, S.-H.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.

(54) (a) Generated by reduction of $VCl_3(THF)_3$ with zinc dust: Freudenberger, J. H.; Konradi, A. W.; Pedersen, S. F. *J. Am. Chem. Soc.* **1989**, *111*, 8014. (b) Kammermeier, B.; Beck, G.; Jacobi, D.; Jendralla, H. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 685. (c) This complex has been characterized by X-ray crystallography: Cotton, A. F.; Duraj, S. A.; Roth, W. J. *Inorg. Chem.* **1985**, *24*, 913.

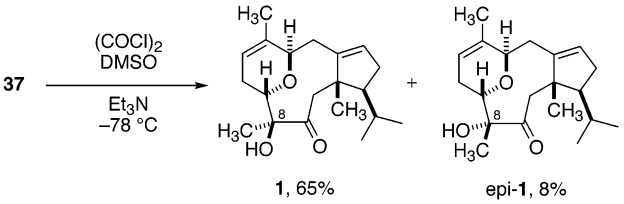
Scheme 9



Scheme 10



Scheme 11



reaction.[55] In our case, the stereochemistry of the major cis-diol was conclusively demonstrated by single-crystal X-ray analysis upon conversion of **33** to the monobenzoate **34**.[56]

At this juncture, completion of the synthesis required the production of a tertiary alcohol at C_8 by the installation of a methyl group corresponding to C_{17}. Inspection of a model based on the rigid, tricyclic **33** asserted that attack of a methyl carbanion at a C_8 ketone would most likely approach from the β-face, providing material epimeric to the natural product. Issues of stereochemistry and the overall inefficiency of sequential oxidations at C_8 and C_9 of **33** prompted the early incorporation of the C_{17} methyl group in the dihydropyran component **2b**.[57]

Encouraged by the stereoselectivity of the vanadium-reductive ring closure, we explored the use of the analogous C_8 methyl ketone. The allylation reaction with the ethyl acetals **2b** proceeded with complete diastereoselectivity as previously described to give the *trans*-dihydropyran **35** in 87% yield (Scheme 9). Deprotection of both C_8 and C_9 protecting units in **35** was effectively executed in good yield upon treatment with sulfuric acid in methanol, and the Swern oxidation gave a single keto aldehyde **36**. Since base-induced epimerization (at C_7) was clearly feasible, an X-ray diffraction study of the low-melting **36** was undertaken, confirming the stereochemistry of the *trans*-2,6-disubstituted dihydropyran.

Unfortunately, treatment under the conditions previously described for the vanadyl-promoted coupling led to the recovery of **36** and only traces of diol product. Successful reductive ring closure was accomplished in excellent yield with $TiCl_3$/Zn(Cu) in DME, providing diol **37** as a mixture of four diastereomers (Scheme 10).[58] Olefinic products generally derived from the McMurry conditions are not observed in our case, a fact which may be attributed to the high degree of ring strain introduced by further reductive eliminations. While yields were uniformly excellent, the ratio of diastereomeric products varied with subtle changes. These experiences significantly contrast with the problematic and often low-yielding formation of diols via the McMurry cyclization as exemplified in the synthesis of taxol.[59] Our careful monitoring of concentration, rate of addition of **36**, and solvent purification reproducibly provided 85% yields of **37a**, **37b**, **37c**, and **37d** in a ratio of 8:2:1:1, respectively.

Since the separation of diol isomers was impractical, trial oxidations of the mixture demonstrated that activated DMSO reagents (oxalyl chloride, DMSO;[53] TFAA, DMSO;[60] and SO_3•pyridine[61]) promoted formation of two separable ketones without C−C bond cleavage. Mild oxidations with TPAP, Dess−Martin, and TEMPO reagents resulted in glycol cleavage to **36**. The Swern oxidation was accompanied by methylthiomethyl ether formation,[62,63] as well as some decomposition with prolonged reaction times. To avoid this problem, oxidations were quenched at an estimated point of 70−80% completion, and the readily separated diol mixture was resubmitted. The recombination of ketone products, followed by flash silica gel chromatography, led to synthetic **1** in 65% yield and a small amount of the C_8 epimer (Scheme 11). All comparisons of spectra, and optical

(55) (a) Additional examples of selectivity: Konradi, A. W.; Pedersen, S. F. *J. Org. Chem.* **1992**, *57*, 28. (b) Banfi, L.; Guanti, G.; Basso, A. *Eur. J. Org. Chem.* **2000**, 939.

(56) Benzoate **34** is probably formed by acylation of the less hindered C_8 alcohol and internal acyl transfer. The X-ray data also confirmed the absolute stereochemistry of **9** arising from the CBS reduction.

(57) Our inability to produce the C_8/C_9 diketone is most likely due to ring strain.

(58) (a) McMurry, J. E.; Lectka, T.; Rico, J. G. *J. Org. Chem.* **1989**, *54*, 3748. (b) For recent reviews: Ephritikhine, M. *J. Chem. Soc., Chem. Commun.* **1998**, 2549. (c) Fürstner, A.; Bogdanovic, B. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2442. (d) Lectka, T. The McMurry Reaction. In *Active Metals. Preparation, Characterization, Applications*; Fürstner, A., Ed.; VCH Publishers: New York, 1995; pp 85−131.

(59) (a) Nicolaou, K. C.; Yang, Z.; Liu, J.-J.; Nantermet, P. G.; Claiborne, C. F.; Renaud, J.; Guy, R. K.; Shibayama, K. *J. Am. Chem. Soc.* **1995**, *117*, 645. (b) For other McMurry coupling reactions of diketones and keto aldehydes: McMurry, J. E.; Dushin, R. G. *J. Am. Chem. Soc.* **1990**, *112*, 6942. (c) Mukaiyama, T.; Shiina, I.; Iwadare, H.; Saitoh, M.; Nishimura, T.; Ohkawa, N.; Sakoh, H.; Nishimura, K.; Tani, Y.; Hasegawa, M.; Yamada, K.; Saitoh, K. *Chem. Eur. J.* **1999**, *5*, 121.

(60) Omura, K.; Sharma, A. K.; Swern, D. *J. Org. Chem.* **1976**, *41*, 957.

(61) (a) Parikh, J. R.; Doering, W. von E. *J. Am. Chem. Soc.* **1967**, *89*, 5505. (b) Tidwell, T. T. Dimethyl Sulfoxide-Sulfur Trioxide/Pyridine. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; John Wiley and Sons: Chichester, England, 1995; Vol. 3, pp 2156−2157.

(62) (a) Moffatt, J. G.; Pfitzer, K. E. *J. Am. Chem. Soc.* **1965**, *87*, 5670. (b) Johnson, C. E.; Phillips, W. G. *J. Am. Chem. Soc.* **1969**, *91*, 682. (c) Corey, E. J.; Kim, C. U. *J. Am. Chem. Soc.* **1972**, *94*, 7586. (d) Hendrickson, J. B.; Schwartzman, S. M. *Tetrahedron Lett.* **1975**, *4*, 273.

(63) Williams, D. R.; Klingler, F. D.; Dabral, V. *Tetrahedron Lett.* **1988**, *29*, 3415.

rotations, with data obtained for authentic material confirmed the major ketone to be synthetic (+)-4,5-deoxyneodolabelline.[64]

One postscript to this study describes efforts which were undertaken to confirm the stereochemical identities of diols **37a**−**d**. Information gathered from the X-ray study of **34**, and molecular modeling of the ketone **1**, reveals a rigid ring system in which the C_9 carbonyl clearly presents an endo (α)- and exo (β)-face. Thus, sterically demanding hydride reagents permit the stereoselective reduction of **1**. As expected, reduction of synthetic **1** with less selective sodium borohydride (EtOH, 0 °C) gave the mix of epimeric diols **37a** and **37c** in a 1:3 ratio, identifying the *cis*-diol **37a** as the minor reduction diastereomer. This parallels observations reported by Kobayashi for the sodium borohydride reduction of neodolabelline.[16] Pinacol product **37b** is not observed upon hydride reductions. However, similarities of proton NMR coupling of the C_9 hydrogen of **37b** with the adjacent diastereotopic methylene were recognized from the previous characterization of **33**. Overall, these studies supported a consistent rationale for the assignments of Scheme 10, leading to formation of the natural product.

In conclusion, the total synthesis of (+)-4,5-deoxyneodolabelline (**1**) has been achieved in 16 steps along the longest linear pathway with an overall yield of 4.5%. Together with a previous synthesis of neodolabellenol, our work presents the first successful strategies for the construction of diterpenes of the neodolabelline class. The synthesis pathway is particularly notable for the high level of atom efficiency and remarkable stereoconvergence.

(64) We thank Professor Bruce F. Bowden, James Cook University, School of Pharmacy and Molecular Sciences, Queensland 4811, Australia, for providing spectra and COSY NMR data for naturally occurring **1**.

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Note Added after ASAP: In the version published on the Web 1/23/2003, eq 1 and Table 2 contained errors. The final Web version published 2/3/2003 and the print version are correct.

Supporting Information Available: Experimental procedures and product characterizations for all new compounds of the synthesis route from Schemes 2−6 and compounds **30** through **37**, general procedures for the hetero Diels−Alder reaction and Luche reduction of Scheme 7 and characterizations of **23a**−**i** and **26**, complete characterizations of synthetic **1** and **epi-1** with ^{1}H NMR and ^{13}C NMR spectra, X-ray crystallographic data for **34** and **36** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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