Toward the Development of a General Chiral Auxiliary. 5. High Diastereofacial Selectivity in Cycloadditions with Trienol Silyl Ethers: An Application to an Enantioselective Synthesis of (−)-Cassioside

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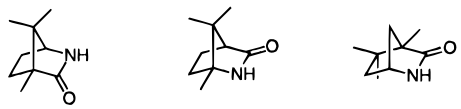
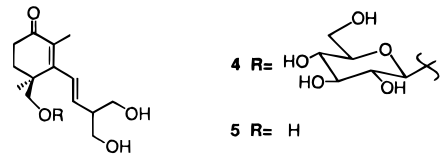
As part of a program directed at the development of covalently bound and catalytic controllers for the diastereofacially selective construction of carbon−carbon bonds,[1] we have developed a family of terpene-derived bicyclic lactams **1**−**3** useful as chiral controller molecules in a variety of applications.[2,3] These controller molecules have proven particularly valuable for the diastereofacially selective construction of quaternary carbon centers *via* [4 + 2] cycloaddition reactions, a significant shortcoming of a number of the most widely employed chiral auxiliaries.[1] Nevertheless, limitations in the scope of cycloaddition methodology using **1**−**3** were still apparent. Use of highly reactive oxygen-substituted dienes has not been generally possible, although a few isolated cases have been reported, owing principally to the sensitivity of the dienes to the Lewis acids required to catalyze the cycloaddition and to the lower diastereofacial selectivity generally observed.[2,4,5] We have addressed these problems by appropriate choice of protecting groups for the dienes and modifications to the Lewis acids that minimize the tendency toward destruction of the diene.



1 **2** **3**

We now report the successful use of suitably protected oxygenated trienes in an application to the first synthesis of the potent antiulcerogenic terpene glycoside (−)-cassioside (**4**),[6] isolated from the aqueous extract of the *Cinnamomi* cortex and characterized by a Japanese group in 1988.[6] Owing to its biological activity and its scarcity in nature, several syntheses of the aglycon (+)-cassiol **5**, which also exhibits very strong antiulcerogenic properties, have appeared.[7,8] These studies include a conceptually related synthesis by Corey that appeared as our effort was nearing completion.[5]



4 R=

5 R= H

Our strategy focused on the enantioselective construction of the quaternary center using an asymmetric Diels−Alder reaction of the chiral dienophile **6**, prepared from the controller lactam **7** (*ent*-**1** obtained from 1(*S*)-camphor) and tris[(triisopropylsilyl)oxy] diene **8** (Scheme 1). Beginning with known aldehyde **9**,[9] two consecutive Wittig reactions using (formylmethylene)triphenylphosphorane and (1-acetylethylidene)triphenylphosphorane[10] afforded 60% of the *E*,*E* dienone **10** accompanied by less than 5% of a mixture of *Z* isomers after purification by chromatography. Hydrolysis of the acetonide in **10** using wet acidic silica gel in CH_2Cl_2, followed by silylation of the resulting keto diol with TIPSOTf and triethylamine, provided the desired oxygenated triene **8** in >99% yield over two steps.

Owing to the acid lability of triene **8**, the crucial Lewis acid-catalyzed Diels−Alder reaction between **6** and **8** gave very poor yields of cycloadduct with a wide range of Lewis acids.[11] Recently, the $TiCl_4$−$SbPh_3$ complex had been reported to be a superior Lewis acid promoter for acid-sensitive substrates, apparently by minimizing the presence of free $TiCl_4$ in solution.[12] When the $TiCl_4$−$SbPh_3$ complex was employed for the cycloaddition of **6** and **8** in the presence of 1 equiv of $(CH_3)_3Al$ as a proton scavenger, decomposition of triene **8** was virtually eliminated, affording a mixture of two diastereomeric cycloadducts **11** and **12** (11:1, endo/exo) in 89% yield *with complete diastereofacial selectivity within detection limits*.[5,13] The absolute stereochemistry of the major diastereomer **11** was determined by treatment of a mixture of **11** and **12** with TBAF in THF at −78 °C and conversion of the resulting diol with $(CH_3)_2C(OCH_3)_2$ and acid in acetone to the nicely crystalline acetonide **13** whose structure and absolute stereochemistry was confirmed by single-crystal X-ray analysis.[14]

Having firmly established the absolute stereochemistry of **11**, reduction of the mixture of **11** and **12** with $LiBH_4$ in THF gave rise to a mixture of the related alcohols and recovered auxiliary **7** from which **14** was separated by chromatography in 72% yield (Scheme 2). Conformational analysis of alcohol **14** suggested that the neopentyl hydroxyl group was extremely hindered. Indeed, glycosidation of **14** (and more advanced intermediates) failed using a variety of commonly used glycosidation methods.[15] The choice of the protecting group employed for the glucose unit also proved to be crucial. The Kahne

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(2) (a) Boeckman, R. K., Jr.; Connell, B. T. *J. Am. Chem. Soc.* **1995**, *117*, 12368. (b) Boeckman, R. K., Jr.; Johnson, A. T.; Musselman, R. A. *Tetrahedron Lett.* **1994**, *35*, 8521. (c) Boeckman, R. K., Jr.; Nelson, S. G.; Gaul, M. D. *J. Am. Chem. Soc.* **1992**, *114*, 2258.

(3) Boeckman, R. K., Jr.; Wrobleski, S. T. *J. Org. Chem.* **1996**, *61*, submitted.

(4) Oppolzer, W.; Seletsky, B. M.; Bernardinelli, G. *Tetrahedron Lett.* **1994**, *35*, 3509.

(5) Conceptually related studies toward (+)-cassiol were reported during the course of our work: Corey, E. J.; Guzman-Perez, A.; Loh, T.-P. *J. Am. Chem. Soc.* **1994**, *116*, 3611.

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(7) (a) Takemoto, T.; Fukaya, C.; Yokoyama, K. *Tetrahedron Lett.* **1989**, *30*, 723. (b) Uno, T.; Watanabe, H.; Mori, K. *Tetrahedron* **1990,** *46*, 5563.

(8) Trost, B. M.; Li, Y. *J. Am. Chem. Soc.* **1996**, *118*, 6625.

(9) Bates, H. A.; Farina, J.; Tong, M. *J. Org. Chem.* **1986,** *51*, 2637.

(10) Fujiwara, K. Takahashi, H.; Ohta, M. *Bull. Soc. Chem. Jpn.* **1962**, *35*, 2042.

(11) Among the Lewis acids tested, $TiCl_4$ gave mainly diene decomposition, Et_2AlCl and Me_2AlCl gave poor yields, and $SnCl_4$ showed insufficient reactivity.

(12) Suzuki, I.; Yamamoto, Y. *J. Org. Chem.* **1993**, *58*, 4783.

(13) This conclusion was based upon the observation that reduction of the mixture of diastereomeric cycloadducts **11** and **12** (11:1) afforded a similar mixture of diastereomeric alcohols (~11:1) of which alcohol **14** was the major isomer. If adducts **11** and **12** were both *endo* arising from facial selectivity in reaction with the diene, reduction would have led to enantiomers of **14**.

(14) Details of the single-crystal X-ray analysis of ketone **13** will be published as part of a full account of this work.

(15) For reviews, see: (a) Toshima, K.; Tatsuta, K. *Chem. Rev.* **1993**, *93*, 1503. (b) Schmidt, R. R. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 212. (c) Paulsen, H. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 155.

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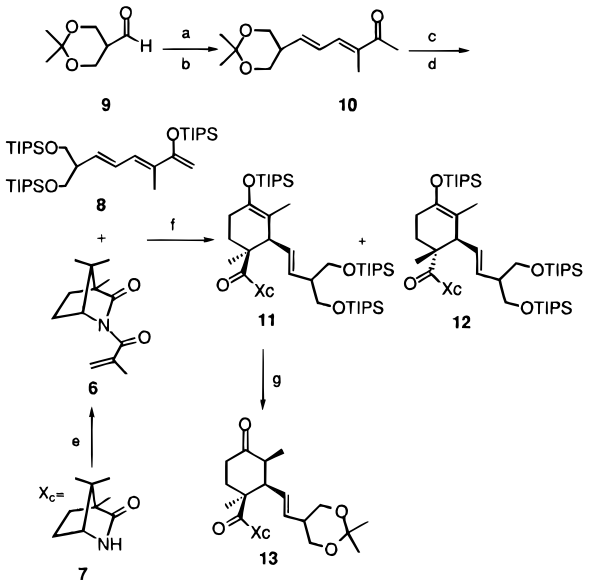
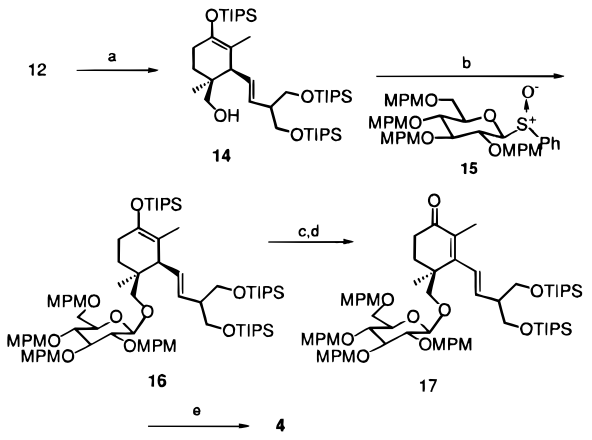
Scheme 1[a]



[a] Key: (a) $Ph_3P{=}CHCHO$ (1 equiv), benzene, reflux; (b) $CH_3COC(=PPh_3)CH_3$ (0.76 equiv), benzene, reflux (60%, two steps); (c) silica gel, CH_2Cl_2/H_2O (9:1), rt (>99%); (d) TIPSOTf (3.2 equiv), Et_3N (4.5 equiv), CH_2Cl_2, rt (100%); (e) *n*-BuLi (1 equiv), THF, 0 °C, then methacryloyl chloride (1.1 equiv), rt, 2 h; (f) **6** (1 equiv), $TiCl_4$ (1 equiv), CH_2Cl_2, −20 °C, 0.25 h then cool to −78 °C, add $SbPh_3$ (1.03 equiv) and $(CH_3)_3Al$ in hexanes (1 equiv), stir 0.5 h, add precooled (−78 °C) **8** (2 equiv) in CH_2Cl_2, stir 48 h; quench with pyridine (89%); (g) **11** (1 equiv), TBAF (xs)/THF/−78 °C, 12 h, then $(CH_3)_2C(OCH_3)_2$ (xs)/H_2SO_4 (catalytic), acetone, rt, 18 h.

Scheme 2[a]



[a] Key: (a) $LiBH_4$ (xs), THF, rt, 48 h (72%); (b) Tf_2O (1.8 equiv), 2,6-di-*tert*-butyl-4-methylpyridine (5.9 equiv), molecular sieves (4 Å), **15** (2.0 equiv), CH_2Cl_2, −90 °C (50%); (c) $Pd(OAc)_2$ (1.2 equiv), AgOTf (1.2 equiv), I_2 (1.0 equiv), **16** (1.0 equiv), $CH_3CN{-}CH_2Cl_2$ (1:9), rt; (d) Et_3N (xs), NaI (xs), acetone, rt (60% over two steps); (e) CAN (9.2 equiv), $CH_3CN{-}H_2O$ (1:9) (80%).

method using tetrabenzylglucose sulfoxide activated with triflic anhydride did provide the required β glycoside in about 40−50% yield, but cleavage of the benzyl protecting groups failed in the presence of unsaturation.[16]

The problem was eventually overcome by modification of the protecting group scheme. Thus, the tetrakis(*p*-methoxybenzyl)glucose sulfoxides **15** (MPM glucose sulfoxides) were prepared.[17] Activation of **15** with Tf_2O in CH_2Cl_2 at −90 °C afforded a very reactive intermediate that proved too unstable for use even at −78 °C. However, addition of the alcohol **14** at −90 °C resulted in surprisingly rapid glycosidation that was complete within 30 min to give ~50% yield of a mixture (17:1) of β glycoside **16** and a substance, which could not be obtained in pure form, tentatively assigned as the α glycoside. The enhanced selectivity for β-glycosidation observed using the tetrakis(*p*-methoxybenzyl)glucose sulfoxides **15** as the glycosyl acceptor is noteworthy and can probably be attributed to the high reactivity of the activated intermediate even at very low temperature, possibly involving participation of the adjacent MPM ether oxygen. The above modification may prove valuable for the glycosidation of hindered alcohols where functional group compatibility precludes use of benzyl or pivaloyl protecting groups.

The conversion of β glycoside **16** to (−)-cassioside (**4**) was completed by iodination **16** using AgOTf, I_2, and $Pd(OAc)_2$, followed by treatment of the resulting sensitive α-iodo ketone intermediate with Et_3N and NaI to provide the enone glycoside **17** in an unoptimized 60% yield over two steps. Use of $Pd(OAc)_2$ in the iodination of **16** has been found to enhance the stereo- and regioselectivity of the iodination process, possibly *via* initial formation of an α-pallado ketone intermediate.[18] Treatment of enone glycoside **17** with ceric ammonium nitrate (CAN)[19] afforded oxidative cleavage of the *p*-methoxybenzyl groups with concomitant cleavage of the TIPS ethers, providing synthetic (−)-cassioside (**4**) $[\alpha]^{25}_D$ −25.1 (*c* 0.6, CH_3OH) (lit.[6] $[\alpha]^{25}_D$ −25.2 (*c* 0.5, CH_3OH) in 80% yield.[20,21]

The successful implementation of the asymmetric Diels−Alder reaction of TIPS-protected trienolsilyl ethers catalyzed by $TiCl_4{-}SbPh_3$ coupled with glycosidation using *p*-methoxybenzyl (MPM)-protected carbohydrate sulfoxides resulted in the realization of a concise synthetic sequence to (−)-**4** consisting of nine steps with an overall yield of ~14%.

Acknowledgment. We are extremely grateful to the National Institute of General Medical Sciences (NIGMS) and the National Cancer Institute (NCI) of the National Institutes of Health for research grants (GM-29290, GM-30345, and CA-29108) in support of these studies.

Supporting Information Available: Experimental procedures and characterization data for compounds **4**, **6**, **8**, **10**, **11**, and **13**−**17** and an ORTEP drawing of the X-ray model for **13** (7 pages).

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(17) Tetrakis(*p*-methoxybenzyl)glucosylphenyl sulfoxides **15** were prepared from tetraacetyl-β-thiophenylglucoside[22] as follows: (1) K_2CO_3 (catalytic), CH_3OH, then NaH (4 equiv), 4-CH_3OPhCH_2Cl (4 equiv), DMF, rt (4 h) → 100 °C (2 h) (74%); (2) *m*-CPBA (1 equiv), CH_2Cl_2, −78 °C (2 h) → rt (12 h) (96%).

(18) A number of mechanistic pathways can be envisioned for this transformation in which Pd(II) can play a role. Since TIPS enol ethers are generally unreactive under conditions used for oxidation of TMS enol silyl ethers to enones,[23] it is conceivable that oxypalladation with concommitant desilylation occurs, followed by oxidative addition of I_2 and reductive elimination to the α-iodo ketone. This pathway is consistent with the observation that the intermediate α-iodo ketone has the iodine *syn* to the hydrogen on the β carbon bearing the alkenyl side chain.

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(21) The spectral characteristics and optical rotation of synthetic (−)-**4** were consistent with the published data,[6] as were the characteristics of (+)-cassiol, which was obtained from **14** by sequential acetylation, iodination/elimination, and deprotection. Attempted glycosidation of suitably protected derivatives of (+)-cassiol was unsuccessful in our hands.

(22) Ferrier, R. J.; Furneaux, R. H. *Methods Carbohydr. Chem.* **1980**, *8*, 251.

(23) Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011.