JOC Article

Connective Synthesis of Polysubstituted Tetrahydropyrans by a Novel and Stereocontrolled Metallo-ene/Intramolecular Sakurai Cyclization Sequence

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A novel methodology based upon the allylmetalation step followed by an Intramolecular Sakurai Cyclization (IMSC) provides an efficient access to a variety of tetrahydropyran derivatives. This new strategy nicely complements our initial protocol that embodied a tandem ene reaction/IMSC sequence. Both mono- and dihydroxy-tetrahydropyrans could be easily assembled with complete stereocontrol at the various chiral centers.

Introduction

Numerous natural products from marine microorganisms possess a fascinating and synthetically challenging structural framework. Their diversity, paucity, and often remarkable biological properties have spurred the interest of the synthetic community, resulting over the years in the development of many elegant approaches toward their total synthesis.[1] The microorganisms responsible for the biosynthesis of such architecturally complex molecular skeletons are varied, but the genus *amphidium* appears to be especially productive.[2] In particular, *amphidinium klebsii* was found to produce amphidinol 1, whose structure has been revealed recently.[3] Amphidinol 1 was the first member of a new family of closely related polyhydroxy-polyenes encompassing nowadays eight derivatives (amphidinols 1−8).[4] Unfortunately, the minute quantity of material isolated from natural sources has plagued the determination of the relative and absolute configuration of the various stereocenters present on the amphidinol backbone and only the "flat" structure could be deduced from numerous spectroscopic experiments. Recently, a tridimensionnal structure has been proposed for amphidinol 3, one of the simplest members of this family (Figure 1).[5]

Amphidinols exhibit promising antifungal, hemolytic, cytotoxic, ichtyologic, and surfactant properties, believed to be associated with the ability of the polyene side chain to perturb plasmic membranes. It is also interesting to note that amphidinols also possess, embedded in their complex architectural framework, two or three dihydroxylated tetrahydropyran subunits. These substructures constitute ubiquitous fragments of many other natural products from marine or terrestrial origin. It is therefore not surprising that a large number of inventive and reliable strategies have been designed for the construction of stereodefined tetrahydropyrans.[6] Our laboratory has also been active in this area and several novel and concise methodologies for the rapid assembly of such interesting heterocycles have been reported over the years. More recently, we have disclosed a new multicomponent condensation strategy, embodying an ene reaction and an Intramolecular Sakurai Cyclization (IMSC), for the stereocontrolled synthesis of polysubstituted tetrahydropyran derivatives (Scheme 1).[7]

Our approach involves an initial ene reaction between an aldehyde and the allylsilane **1**, promoted by Et_2AlCl, leading efficiently to the (*Z*)-homoallylic alcohol **2** with complete control of the geometry of the double bond. Subsequent condensation of **2** with another aldehyde

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(5) Murata, M.; Matsuoka, S.; Matsumori, N.; Paul, G. K.; Tachibana, K. *J. Am. Chem. Soc.* **1999**, *121*, 870.

(6) For excellent reviews, see: (a) Boivin, T. L. B. *Tetrahedron* **1987**, *43*, 3309. (b) Elliott, M. C. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1291 and references therein.

(7) (a) Markó, I. E.; Bayston, D. J. *Tetrahedron Lett.* **1993**, *34*, 6595. (b) Markó, I. E.; Plancher, J.-M. *Tetrahedron Lett.* **1999**, *40*, 5259. For similar strategies based upon the capture of an oxonium cation intermediate by allyl- or vinylsilanes, see: (a) Johnson, W. S. *Acc. Chem. Res.* **1968**, *1*, 1. (b) Chow, H.-F.; Fleming, I. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1815. (c) Coppi, L.; Ricci, A.; Taddei, M. *J. Org. Chem.* **1988**, *53*, 911. (d) Wei, Z. Y.; Wang, D.; Li, J. S.; Chan, T. H. *J. Org. Chem.* **1989**, *54*, 5768. (e) Mohr, P. *Tetrahedron Lett.* **1995**, *36*, 2453. (f) Semeyn, C.; Blaauw, R. H.; Hiemstra, H.; Speckamp, W. N. *J. Org. Chem.* **1997**, *62*, 3426. (g) Suginome, M.; Iwanami, T.; Ito, Y. *J. Org. Chem.* **1998**, *63*, 6096. (h) Yang, J.; Viswanathan, G. S.; Li, C. J. *Tetrahedron Lett.* **1999**, *40*, 1627. (i) Viswanathan, G. S.; Yang, J.; Li, C.-J. *Org. Lett.* **1999**, *1*, 993. (j) Yadav, J. S.; Subba Reddy, B. V.; Mahesh Kumar, G.; Murthy, C. V. S. R. *Tetrahedron Lett.* **2001**, *42*, 89. (k) Markó, I. E.; Mekhalfia, A.; Bayston, D. J.; Adams, H. *J. Org. Chem.* **1992**, *57*, 2211. (l) Markó, I. E.; Bayston, D. J. *Synthesis* **1996**, 297. (m) Markó, I. E.; Chellé, F. *Tetrahedron Lett.* **1997**, *38*, 2895.

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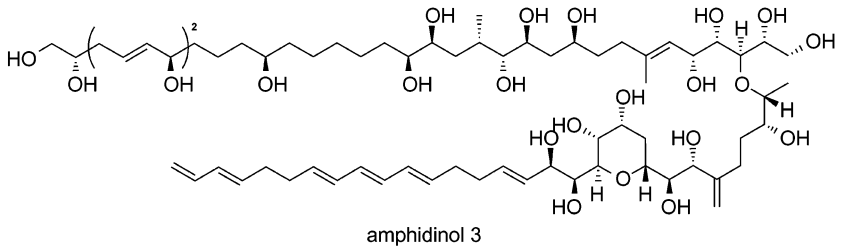
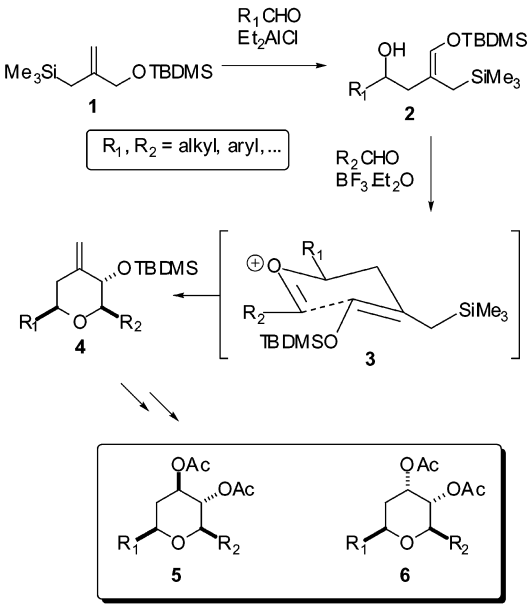


FIGURE 1. Structure and absolute configuration of amphidinol **3**.

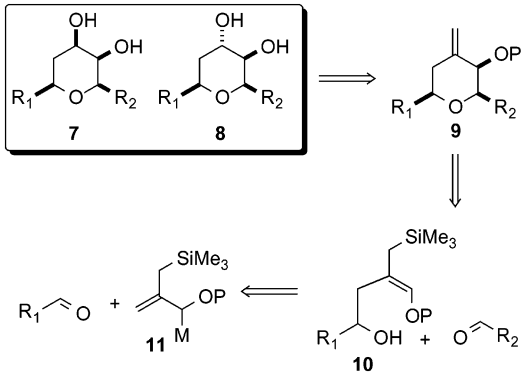
SCHEME 1. Ene−IMSC Strategy



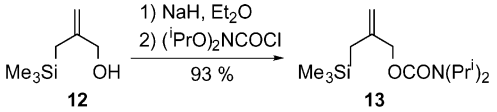
affords the polysubstituted *exo*-methylene tetrahydropyran **4** in good yields and with total stereocontrol. The second reaction is believed to proceed through the formation of the oxonium cation **3** that undergoes an intramolecular addition of the allylsilane moiety via a chairlike transition state, in agreement with the exclusive equatorial disposition of the substituents in the final product. Subsequent ozonolysis of the exocyclic double bond of **4**, followed by stereocontrolled reduction of the corresponding ketone gives access to the two stereocomplementary dihydroxy-tetrahydropyrans **5** and **6**.

As part of our efforts toward the preparation of various analogues of the tetrahydropyran fragments of amphidinols and in order to unambiguously establish the relative and absolute stereochemistry of these subunits, a concise and flexible access to the diastereomeric diols **7** and **8** (Scheme 2) proved mandatory. According to our previous approach, these two diols could be obtained by oxidation of the exocyclic double bond of tetrahydropyran **9**, followed by a stereoselective reduction of the corresponding ketone. Heterocycle **9** could in turn be prepared by an IMSC cyclization starting from the homoallylic alcohol **10**. Unfortunately, the previously employed ene reaction gives selective access to the (*Z*)-olefin and is therefore not suitable for preparing the desired (*E*)-homoallylic alcohol **10**. Therefore, we envisaged the use of allylmetal intermediate **11** for the selective synthesis of **10**.[8]

SCHEME 2. Retrosynthetic Analysis



SCHEME 3. Synthesis of Allylcarbamate 13



Results and Discussion[9]

Stereoselective Allyltitanation of Aldehydes. Carbamate substituents are known to facilitate the formation of stable allylic anions and to favor stereoselective reactions of these intermediates with various electrophiles.[10] The synthesis of allylsilane **13**, bearing a diisopropylcarbamate directing group, was thus initiated. Deprotonation of allylic alcohol **12** (prepared according to the literature[11]) by sodium hydride, followed by treatment of the resulting alkoxide with diisopropylcarbamoyl chloride provided an efficient access to **13** (Scheme 3). After thorough experimentation, it was found that deprotonation of **13** with *sec*-BuLi, followed by transmetalation of the resulting allyllithium species by titanium tetraisopropoxide and addition of an aldehyde gave the desired homoallylic alcohol **16** as the single (*E*)-isomer (Scheme 4). This selectivity is believed to result from the prefer-

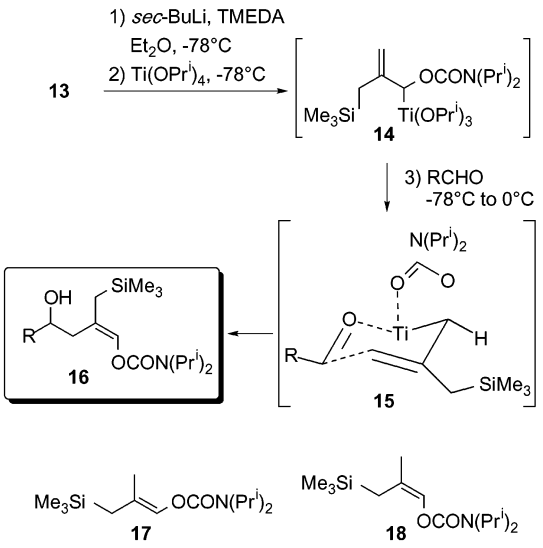
(8) For excellent reviews on allylmetal species bearing α-alkoxy substituents, see: (a) Yamamoto, Y. *Heteroatom-stabilized allylic anions*. In Trost, B. M.; Fleming, I., Eds. *Comprehensive Organic Synthesis*; Pergamon Press: Oxford, UK, 1991; Vol. 2, p 55. (b) Katritzky, A. R.; Piffl, M.; Lang, H.; Anders, E. *Chem. Rev.* **1999**, *99*, 665.

(9) Some results have been previously reported in a communication: Markó, I. E.; Leroy, B. *Tetrahedron Lett.* **2000**, *41*, 7225.

(10) (a) Hoppe, D.; Hanko, R.; Brönneke, A.; Lichtenberg, A. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 1024. (b) Hoppe, D. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 932. (c) Hoppe, D.; Krämer, T. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 160. (d) Zschage, O.; Hoppe, D. *Tetrahedron* **1992**, *48*, 5657. (e) Paulsen, H.; Graeve, C.; Hoppe, D. *Synthesis* **1996**, 141. (f) Hoppe, D.; Hense, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2283.

(11) Trost, B. M.; Chan, D. M. T.; Nanninga, T. N. *Org. Synth.* **1984**, *62*, 58.

SCHEME 4. Synthesis of (*E*)-Enolcarbamates

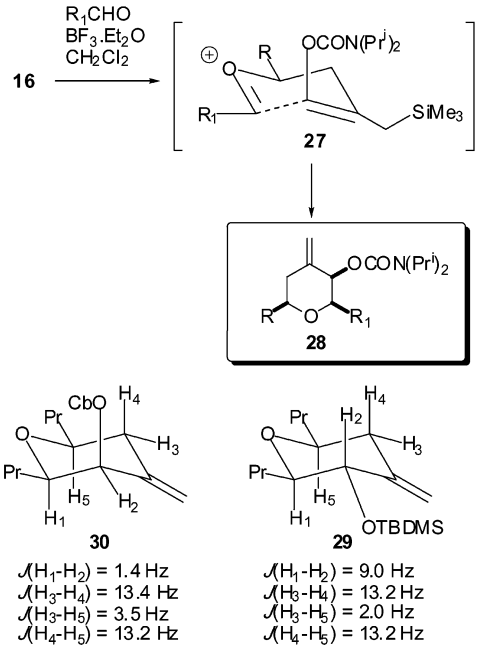


ential axial position of the carbamate group in the transition state **15**, allowing a more efficient coordination of the metal center. Among the numerous experimental conditions used to achieve this transformation, diethyl ether proved to be the solvent of choice, and *sec*-BuLi was found to give slightly better results than *n*-BuLi. While the deprotonation and the transmetalation steps are effected at low temperature (−78°C), it is crucial to increase the temperature rapidly to 0°C after the addition of the aldehyde in order to maximize the yields and to minimize the formation of byproducts such as the isomeric olefins **17** and **18**. These compounds probably originate from the protonation of the unreacted alkyltitanium intermediate **14**.

This methodology proved to be general and applicable to a wide range of aldehydes, as illustrated in Table 1. Primary, secondary, and tertiary aliphatic aldehydes reacted smoothly (entries 1−3), and so did unsaturated aldehydes (entries 4 and 5). In some cases, complete diastereoselectivity was observed, as exemplified by the condensation of **13** with bromovaleraldehyde, affording the *anti*-adduct **24** as the only product (entry 6). In contrast, α-hydroxy- or α,*β*-dihydroxyaldehydes formed the desired adducts with only modest stereocontrol (entries 7 and 8). This low selectivity might be due to a competition between chelated and nonchelated transition states.[12] It is noteworthy that, in all cases, only the (*E*)-geometric isomer of the enolcarbamate double bond is observed.

Intramolecular Sakurai Cyclization (IMSC). Having developed a ready access to the desired (*E*)-enolcarbamates, we next turned our attention to the crucial Intramolecular Sakurai Cyclization. It was rapidly found that BF_3·Et_2O smoothly promotes this transformation, generating efficiently the expected tetrahydropyrans **28** with exquisite diastereocontrol (Scheme 5). We were delighted to find that the carbamate substituent adopted, in every case, an axial disposition, in agreement with the geometry of the starting olefin **16** and the proposed chairlike transition state **27**. The stereochemistry of the carbamate substituent was clearly established by comparing the values of the coupling constants between the newly formed heterocyle **30** and the previously prepared

SCHEME 5. Synthesis and Stereochemistry of Tetrahydropyrans



tetrahydropyran **29** bearing a silyloxy group in the equatorial position.[71]

This reaction tolerates a wide range of homoallylic alcohols and aldehydes, as exemplified in Table 2. Alkyl groups on both reactants may be simple (entries 1 and 2) or hindered (entry 3). Unsaturated substituents are tolerated as well (entry 4), giving access, for example, to trienic tetrahydropyran **33**. Finally, the brominated derivative **24** affords the interesting heterocycle **34** in good yield (entry 5).

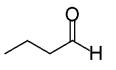
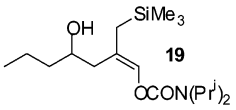
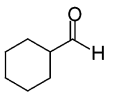
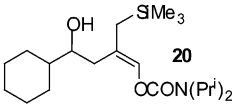
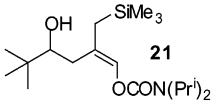
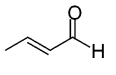
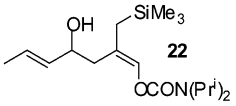
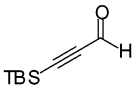
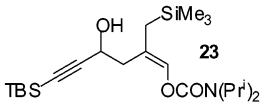
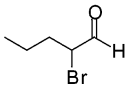
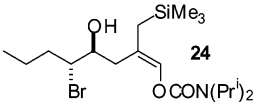
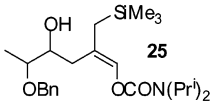
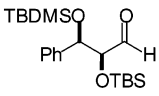
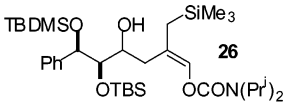
The case of the propargyl-substituted allylcarbamate **23** is slightly different. Indeed, the condensation of this substrate with cinnamaldehyde led to a mixture of the two epimeric tetrahydropyrans **35** and **36** (Scheme 6). Though still largely in favor of the all-*syn* product, this reaction constitutes the first example of a nonstereoselective IMSC cyclization. The reasons for this discrepancy are not yet clear, but other reports in the literature on the particular behavior of acetylenic derivatives tend to suggest a predominant role of electronic interactions.

The use of α-hydroxyaldehydes such as **37** in the IMSC reaction proved to be problematic. Instead of the expected tetrahydropyran **40**, only the homoallylic alcohol **38**, resulting from a direct Sakurai allylation, was obtained (Scheme 7). This particular behavior of α-hydroxyaldehydes originates probably from the difficulty in generating the oxonium intermediate **39** due to the presence of the electron-withdrawing oxygen substituent at the α-position. The cyclization pathway would consequently be disfavored and the direct allylation process takes place.[13] It is noteworthy that **38** is obtained as a single diastereoisomer, of yet unknown relative stereochemistry.

Synthesis of *syn*-Diol. To prepare the stereocomplementary *syn*- and *anti*-diols **7** and **8**, we envisioned

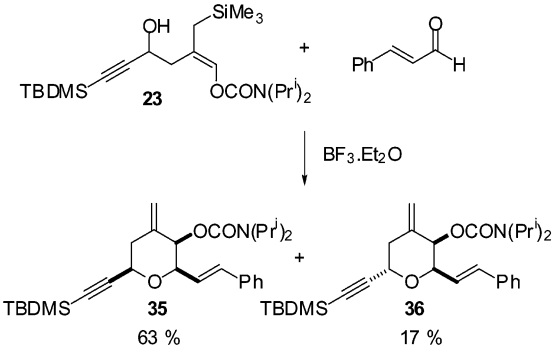
(12) For the effect of oxygenated substituents on stereoselectivity in allyltitanation of aldehydes, see: Martin, S. F.; Li, W. *J. Org. Chem.* **1989**, *54*, 6129.

TABLE 1. Selective Synthesis of Functionnalyzed (*E*)-Enolcarbamates[a]

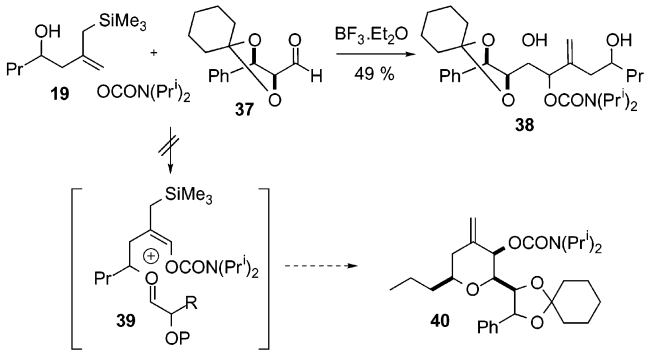
Entry	Aldehyde	Product	Yield[b]	d.e.[c]
1		 **19**	71 %	-
2		 **20**	70 %	-
3		 **21**	66 %	-
4		 **22**	56 %	-
5		 **23**	82 %	-
6		 **24**	77 %	> 99 %
7		 **25**	63 %	24 %
8		 **26**	80 %	18 %

[a] All reactions were carried out according to the general procedure described in Scheme 4. [b] All yields refer to pure, isolated products. [c] d.e. values were measured by ^{1}H NMR spectroscopy.

SCHEME 6 Cyclization of Acetylenic Derivative 23



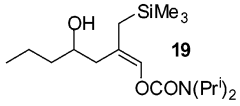
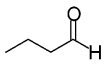
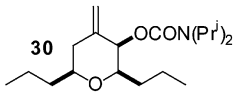
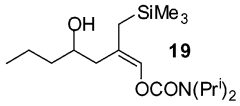
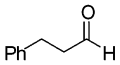
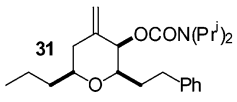
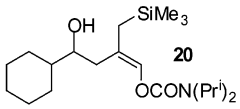
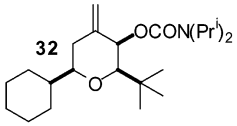
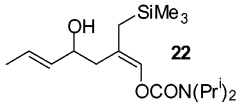
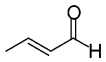
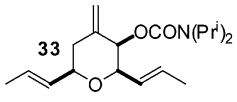
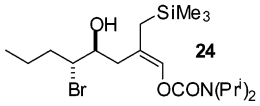
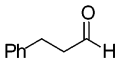
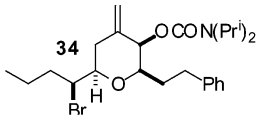
SCHEME 7. Sakurai Reaction with α-Hydroxyaldehyde 37



oxidatively cleaving the exocyclic double bond of tetrahydropyran **30** and reducing the resulting ketone **41** under appropriate conditions. Gratifyingly, ozonolysis of **30**, followed by reductive treatment with dimethyl sulfide afforded quantitatively ketone **41**. This compound was not isolated, but directly submitted to various reductive conditions in order to obtain the *syn*- or the *anti*-dihydroxylated compounds **42** and **43**, corresponding respectively to an axial and an equatorial approach of the reducing agent (Scheme 8).[14] As illustrated in Table 3, the selectivity of this reduction is, in every case, in favor of the *syn* product **42**. This is the expected selectiv-

(13) Similar results have been obtained in our attempts to condense homoallylic alcohols such as **2** with α-hydroxyaldehydes or α,*β*-dihydroxyaldehydes. In these cases, however, degradation is observed instead of the Sakurai addition product. A modified strategy, based upon the use of allylstannane derivatives, allows the introduction of such aldehydes: (a) Leroy, B.; Markó, I. E. *Tetrahedron Lett.* **2001**, *42*, 8685. (b) Leroy, B.; Markó, I. E. *Org. Lett.* **2002**, *4*, 47.

TABLE 2. Intramolecular Sakurai Cyclization of Enolcarbamates[a]

Entry	Substrate	Aldehyde	Product	Yield[b]
1				91 %
2				81 %
3				78 %
4				88 %
5				85 %

[a] All reactions were carried out according to the general procedure described in Scheme 5. [b] All yields refer to pure, isolated products.

SCHEME 8. Synthesis of *syn*-Diol 44

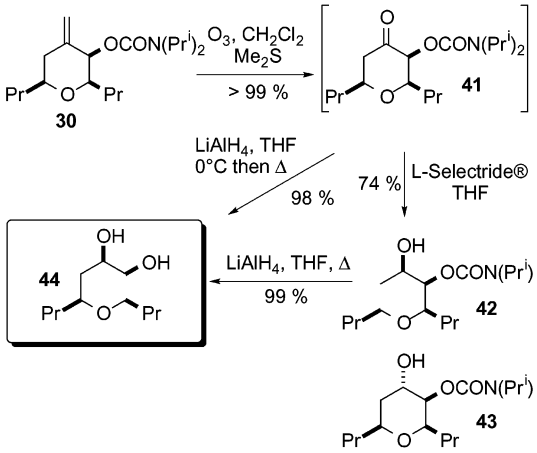


TABLE 3. Reduction of ketone 41

entry	conditions	**42**/**43**[a]	yield,[b] %
1	$NaBH_4$, EtOH	90/10	86
2	BH_3·Me_2S, Et_2O, rt	69/31	86
3	BH_3·Me_2S, Et_2O, −78 °C to rt	83/17	77
4	AlH_3, Et_2O	67/33	66
5	$Zn(BH_4)_2$, Et_2O	90/10	54
6	DIBAL-H, CH_2Cl_2	62/38	91
7	DIBAL-H, toluene	71/29	70
8	L-Selectride, THF	>99/1	74
9	tBuMgCl, MAD, toluene	80/20	70
10	$NaBH_4$, $CeCl_3$·$7H_2O$, THF/MeOH	58/42	35
11	H_2, PtO_2 cat., MeOH		0

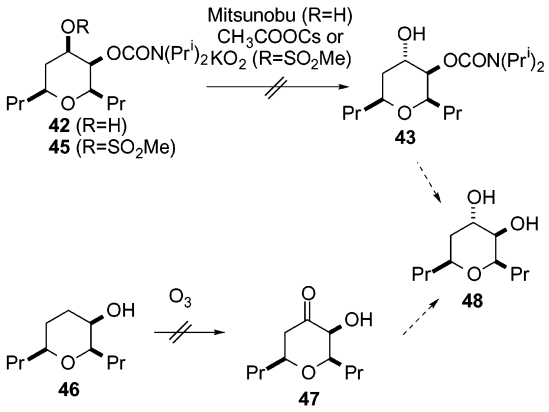
[a] Ratios were determined by ^{1}H NMR spectroscopy of the crude reaction mixture. [b] Combined yields after separation of the two diastereoisomers by column chromatography. Selected *J* values for H_4: **42** (ddd, J = 11.8, 5.0, 3.1 Hz); **43** (q, J = 3.0 Hz).

ity for a small hydride donor such as $NaBH_4$ (entry 1), BH_3 (entries 2 and 3), or AlH_3 (entry 4). However, the carbamate function appears unable to direct the reduction in the presence of a chelating hydride donor such as $Zn(BH_4)_2$ (entry 5). A more sterically hindered reducing agent are normally expected to deliver a hydride from an equatorial approach in the case of configurationally blocked cyclohexanones. However, the use of Dibal-H did not improve the proportion of anti product (entries 6 and 7) and a complete axial selectivity is observed with the bulky L-Selectride (entry 8). The axial, voluminous carbamate group therefore appears to prevent the equatorial approach of the reducing agent. This repulsive steric interaction is believed to be particularly unfavorable in the case of large reagents such as L-Selectride. Attempts to prevent axial reduction by using a bulky coordinating Lewis acid, such as MAD[15] (entry 9) or cerium trichloride (entry 10), met with little success. Though the amount of *anti* product increased, the selectivity still remained in favor of the *syn* compound. Finally, hydrogenation proved to be completely ineffective (entry 11). Although none of the conditions tested provided a selective route to the *anti*-hydroxycarbamate **43**, the *syn* isomer **42** could be prepared in good overall yield. To complete our sequence and ultimately reach *syn*-diol **44**, the deprotection of the carbamate function had to be accomplished. This transformation was smoothly realized by treatment of **42** with LAH, affording finally the desired *syn*-diol **44** in quantitative yield. In an even more efficient procedure,

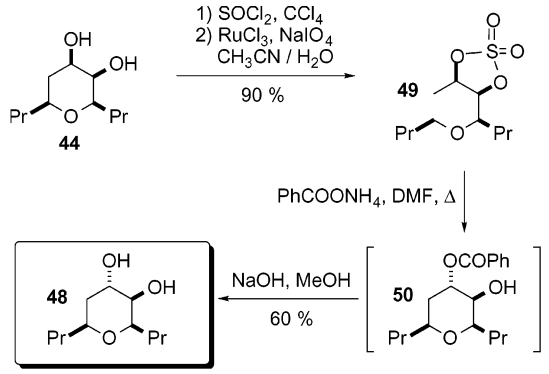
(14) Gung, B. W. *Tetrahedron* **1996**, *52*, 5263.

(15) Maruoka, K.; Itoh, T.; Sakurai, M.; Nonoshita, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1988**, *110*, 3588.

SCHEME 9. Attempted Pathways toward *anti*-Diol 48



SCHEME 10. Synthesis of the *anti*-Diol 48



it was possible to treat ketone **41** directly with an excess of reducing agent to obtain **44** with excellent yield and selectivity.

Synthesis of *anti*-Diol. As mentioned earlier, no reductive conditions were found to prepare selectively the tetrahydropyran **43** possessing an *anti*-diol functionality. Therefore, several strategies to access diol **48** from *syn* compound **42** were explored (Scheme 9). Attempts to invert the alcohol function of compound **42** under Mitsunobu conditions or by displacement of the corresponding mesylate **45** with cesium carbonate or superoxide ion proved to be ineffective. Ozonolysis of tetrahydropyran **46** was attempted to explore the possibility of a directed reduction of the resulting hydroxyketone **47** into **48**. However, ozonolysis of **46** resulted in complete degradation, possibly due to interaction of the axial alcohol with the ozonide intermediate (in stark contrast, the analogous compound with an equatorial alcohol can be ozonolyzed in good yield).[16] These unsuccessful approaches prompted us to focus on an alternative strategy involving cyclic sulfate **49**. According to the protocol described by Sharpless, the efficient transformation of the previously obtained *syn*-diol **44** into the corresponding cyclic sulfate **49** was performed in 90% yield.[17] This activated intermediate was then reacted with ammonium benzoate, in DMF, affording the hydroxyester **50**, which was not isolated but directly hydrolyzed to the desired *anti*-diol **48** by treatment with sodium hydroxide in methanol

(16) For interactions of free alcohols with intermediate ozonides, see: Jung, M. E.; Davidov, P. *Org. Lett.* **2001**, *3*, 627.

(17) Gao, Y.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 7538.

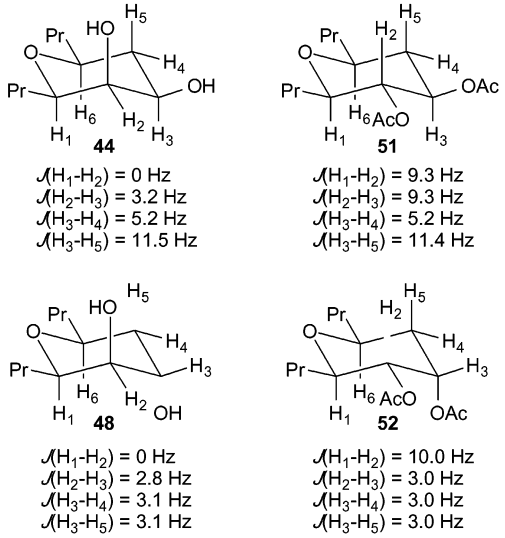
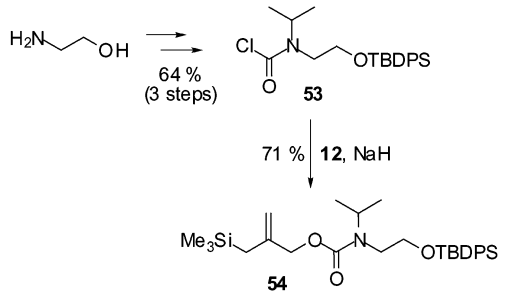


FIGURE 2. Stereochemistry of dihydroxylated tetrahydropyrans.

SCHEME 11. Preparation of Modified Carbamate 54



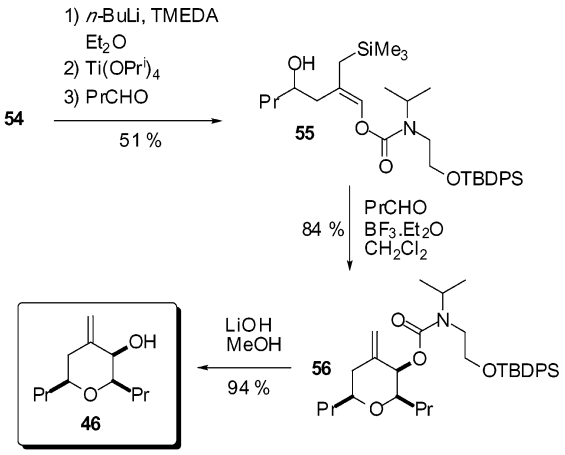
(Scheme 10). The opening of the cyclic sulfate was completely axial selective, no trace of the possible *syn*-hydroxyester contaminant being detected. The stereochemistry of the *syn*- and *anti*-diols **44** and **48** was confirmed by comparison of the proton NMR data with those of the stereocomplementary tetrahydropyrans **51** and **52** (Figure 2).

Deprotection of the Carbamate Moiety. While the routes depicted above afforded an efficient and concise access to diols **44** and **48**, it was also desirable to prepare the corresponding *exo*-methylene tetrahydropyran **46**, bearing an axially oriented alcohol function, by deprotection of the carbamate functionnality of **30**. Unfortunately, none of the classical conditions for deprotection of carbamate (basic, acidic, or reductive) were successful in this case. To circumvent this problem, we turned our attention toward the use of a modified carbamate group described by Hoppe et al.[18] Carbamoyl chloride **53** was prepared, according to the literature, from ethanolamine. Condensation of **53** with alcohol **12** afforded allylcarbamate **54** in good yield (Scheme 11).

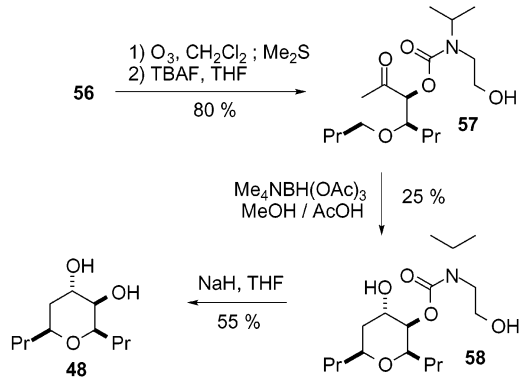
Initial attempts at allyltitanation of butyraldehyde with carbamate **54** proceeded less efficiently than with the diisopropyl analogue **13**. However, the choice of the base proved to be of crucial importance, as *sec*-BuLi gave the expected homoallylic alcohol **55** in only 13% yield.

(18) Derwing, C.; Hoppe, D. *Synthesis* **1996**, 149.

SCHEME 12. Synthesis of Hydroxylated Tetrahydropyran 46



SCHEME 13. Alternative Synthesis of *anti*-Diol 48



We assumed that *sec*-BuLi was a base strong enough to competitively abstract protons next to the nitrogen of the carbamate moiety, leading to degradation.[19] In contrast, the use of a slightly weaker base such as *n*-BuLi provided adduct **55** in a much improved yield of 51% (Scheme 12). The allylic alcohol **55** thus obtained was then subjected to the IMSC reaction with butyraldehyde, affording in excellent yield tetrahydropyran **56**, which was easily deprotected by treatment with lithium hydroxide, allowing for the first time an easy access to hydroxylated heterocycles such as **46**. Moreover, axial carbamate **56** also proved to be an interesting intermediate in the preparation of *anti*-diol **48**. Thus, ozonolysis of **56** followed by fluoride-mediated deprotection afforded hydroxyketone **57** in excellent yield (Scheme 13). At this stage, we speculated that hydroxyl-directed reduction of the ketone function would produce the desired *anti*-hydroxycarbamate **58**. Although such an intramolecularly assisted hydride delivery bears marginal chances of success, it was nevertheless attempted with use of triacetoxyborohydride.[20] Gratifyingly, *anti*-hydroxycarbamate **58** was obtained as a single diastereoisomer, albeit in rather modest yield. Simple treatment of **58** with NaH removed the protecting group, affording *anti*-diol **48**, identical in all respects with a sample prepared by the cyclic sulfate opening protocol.

(19) Beak, P.; Kerrick, S. T.; Wu, S.; Chu, J. *J. Am. Chem. Soc.* **1994**, *116*, 3231.

(20) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560.

Conclusions

In summary, we have developed an efficient access toward new tetrahydropyran units, based upon an allylmetalation protocol followed by an Intramolecular Sakurai Cyclization. This novel strategy nicely complements our initial protocol involving an ene/IMSC sequence. Furthermore, we have demonstrated that mono- and dihydroxylated tetrahydropyrans could be prepared in a highly stereoselective manner. These heterocycles are interesting fragments ubiquitously present in a range of biologically active natural products. Current efforts are now directed toward exploring the application of this novel methodology to the total synthesis of interesting biomolecules, including the amphidinols, and delineating an enantioselective version of this connective strategy.

Experimental Section

Most of the commercially available reagents were used without further purification. Titanium tetraisopropoxide was distilled prior to use. Methylene chloride, acetonitrile, and TMEDA were distilled over calcium hydride. Diethyl ether and THF were distilled over sodium and benzophenone. All glassware was flame dried prior to use and the reactions were carried out under argon atmosphere.

2-Trimethylsilylmethylallyl-diisopropylcarbamate (13). To a suspension of NaH (60% in mineral oil, 833 mg, 20.8 mmol) in diethyl ether (12 mL) at 0 °C was added a solution of alcohol **12** (2 g, 13.9 mmol) in diethyl ether (12 mL). After the mixture was stirred for 30 min at 0 °C, a solution of diisopropylcarbamoyl chloride (4.55 g, 27.8 mmol) in diethyl ether (12 mL) was added and the solution was stirred at room temperature for 18 h. The mixture was poured onto saturated aqueous NH_4Cl (30 mL) and extracted with dichloromethane. The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography over silica gel (petroleum ether/ethyl acetate 30/1) to give **13** as a colorless oil (3.48 g, 93%). IR (neat) 1699, 1645 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 4.85 (1H, q, J = 1.6 Hz), 4.66 (1H, br s), 4.43 (2H, s), 3.61−4.19 (2H, m), 1.52 (2H, s), 1.18 (12H, d, J = 6.2 Hz), 0.02 (9H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 155.93, 143.45, 109.21, 68.64, 46.56, 24.35, 21.70, −0.75; mass spectrum (EI) m/z 271.2 ($M^{\bullet+}$, 82). Anal. Calcd for $C_{14}H_{29}NO_2Si$: C, 61.94; H, 10.77; N, 5.16. Found: C, 61.97; H, 10.88; N, 5.10.

General Procedure for the Preparation of Homoallylic Alcohols. 4-Hydroxy-2-trimethylsilylmethyl-hept-1-enyl-diisopropylcarbamate (19). To a solution of TMEDA (1.12 mL, 7.38 mmol) in diethyl ether (15 mL) at −78°C was added *sec*-BuLi (1.3 M solution in hexane, 5.68 mL, 7.38 mmol) and the resulting solution was stirred 30 min at −78 °C. A solution of allylcarbamate **13** (1 g, 3.69 mmol) in diethyl ether (15 mL) was added dropwise and the solution was stirred 30 min at −78 °C. Titanium tetraisopropoxide (3.27 mL, 11.07 mmol) was added in one portion and the solution was stirred for 30 min at −78 °C. A solution of butyraldehyde (499 μL, 5.54 mmol) in diethyl ether (15 mL) was quickly added and the temperature was allowed to warm rapidly to 0 °C by changing the dry ice/acetone bath with an ice bath immediatly after the addition of the aldehyde. After stirring 15 min at 0°C, the reaction mixture was poured onto 1 N HCl (50 mL) and extracted with diethyl ether (2 × 50 mL). The organic layer was washed with saturated $NaHCO_3$ (40 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography over silica gel (petroleum ether/ethyl acetate 8/1) to give **19** as a colorless oil (901 mg, 71%). IR (neat) 3474, 1700 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 6.79 (1H, s), 3.75−3.94 (3H, m), 2.36 (1H, dd, J = 13.2, 9.3 Hz), 2.09 (1H, dd, J = 13.4, 3.8 Hz), 1.78 (1H, br s), 1.01−1.51 (6H, m), 1.23 (12H, d, J = 6.5 Hz), 0.92 (3H, t, J = 6.1 Hz), 0.04 (9H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 153.94, 132.61,

119.00, 69.92, 46.92, 40.21, 39.31, 21.72, 21.42−21.84, 19.58, 14.82, −0.49; mass spectrum (EI) *m*/*z* 343.3 ($M^{\bullet+}$, 8). Anal. Calcd for $C_{18}H_{37}NO_3Si$: C, 62.93; H, 10.85; N, 4.08. Found: C, 62.95; H, 10.89; N, 4.07.

General Procedure for the Preparation of Tetrahydropyrans. 4-Methylene-2,6-dipropyl-tetrahydropyran-3-yl-diisopropylcarbamate (30). To a solution of alcohol **19** (855 mg, 2.49 mmol) and butyraldehyde (198 mg, 2.74 mmol) in dichloromethane (25 mL) at −78 °C was added slowly $BF_3.Et_2O$ (338 μL, 2.74 mmol). The temperature was allowed to warm to 0 °C over 3 h. The reaction mixture was poured onto saturated $NaHCO_3$ (25 mL) and the aqueous layer was extracted with dichloromethane (2 × 25 mL). The combined organic layers were dried (MgSO4), filtered, and evaporated in vacuo. The residue was purified by column chromatography (silica gel, petroleum ether/ethyl acetate 25/1) to give the tetrahydropyran **30** as a colorless oil (737 mg, 91%). IR (neat) 1693, 1657 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.08 (2H, br s), 4.89 (1H, t, *J* = 1.6 Hz), 3.90−4.23 (1H, m), 3.59−3.72 (1H, m), 3.34 (1H, ddd, *J* = 8.2, 4.5, 1.4 Hz), 3.24−3.32 (1H, m), 2.18 (1H, tt, *J* = 13.2, 1.6 Hz), 2.11 (1H, dd, *J* = 13.4, 3.5 Hz), 1.38−1.66 (8H, m), 1.19 (12H, d, *J* = 6.8 Hz), 0.91 (3H, t, *J* = 7.1 Hz), 0.89 (3H, t, *J* = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.20, 143.23, 113.20, 79.99, 78.43, 74.12, 46.10 (br), 38.42, 37.52, 33.73, 21.20 (br), 18.89, 18.72, 14.03; mass spectrum (EI) *m*/*z* 325.2 ($M^{\bullet+}$, 11). Anal. Calcd for $C_{19}H_{35}NO_3$: C, 70.11; H, 10.84; N, 4.30. Found: C, 70.00; H, 10.81; N, 4.36.

6-[(*tert*-Butyl-dimethyl-silyl)-ethynyl]-4-methylene-2-styryl-tetrahydropyran-3-yl-diisopropylcarbamate (35). IR (neat) 1689, 1439 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.18−7.35 (5H, m), 6.68 (1H, d, *J* = 15.8 Hz), 6.23 (1H, dd, *J* = 15.8, 5.3 Hz), 5.26 (1H, s), 5.24 (1H, s, H-9a), 5.06 (1H, s), 4.26 (1H, dd, *J* = 11.5, 2.9 Hz), 4.15 (1H, d, *J* = 5.3 Hz), 3.92−4.18 (1H, m), 3.58−3.86 (1H, m), 2.71 (1H, bt, *J* = 13.4 Hz), 2.46 (1H, dd, *J* = 13.4, 2.9 Hz), 1.06−1.30 (12H, s), 0.95 (9H, s), 0.13 (3H, s), 0.12 (3H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 154.84, 140.86, 136.88, 131.91, 128.39, 127.50, 126.53, 125.81, 114.92, 104.52, 88.26, 80.65, 73.71, 68.98, 45.94 (br), 38.21, 26.02, 21.01 (br), 16.53, −4.75; mass spectrum (EI) *m*/*z* 481.4 ($M^{\bullet+}$, 2); HRMS calcd for $C_{29}H_{43}NO_3Si$ (EI, $M^{\bullet+}$) 481.3012, found 481.3002.

6-[(*tert*-Butyl-dimethyl-silyl)-ethynyl]-4-methylene-2-styryl-tetrahydropyran-3-yl-diisopropylcarbamate (36). IR (neat) 1691, 1469 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.17−7.35 (5H, m), 6.65 (1H, d, *J* = 16.1 Hz), 6.22 (1H, dd, *J* = 16.1, 5.2 Hz), 5.35 (1H, d, *J* = 1.7 Hz), 5.29 (1H, s), 5.01 (1H, s), 4.96 (1H, dd, *J* = 5.7, 1.9 Hz), 4.74 (1H, dd, *J* = 5.2, 1.8 Hz), 3.59−4.15 (2H, m), 2.89 (1H, dd, *J* = 13.7, 5.7 Hz), 2.28 (1H, dd, *J* = 13.2, 1.7 Hz), 1.13−1.28 (12H, m), 0.94 (9H, s), 0.11 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.79, 138.56, 136.93, 131.71, 128.39, 127.44, 126.43, 125.82, 115.61, 103.04, 90.72, 74.98, 73.99, 66.07, 46.00 (br), 39.94, 26.03, 20.05 (br), 16.44, −4.66; mass spectrum (EI) *m*/*z* 481.2 ($M^{\bullet+}$, 8). Anal. Calcd for $C_{29}H_{43}NO_3Si$: C, 72.30; H, 9.00; N, 2.91. Found: C, 71.98; H, 9.05; N, 2.83.

2-(2-Hydroxy-pentyl)-1-[hydroxy-(3-phenyl-1,4-dioxa-spiro[4.5]dec-2-yl)-methyl]-allyl-diisopropylcarbamate (38). IR (neat) 3411, 1675, 1443 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.41 (2H, d, *J* = 6.9 Hz), 7.27−7.37 (3H, m), 5.27 (1H, br s), 5.10 (1H, s), 5.09 (1H, d, *J* = 7.1 Hz), 5.04 (1H, s), 4.06 (1H, dd, *J* = 8.2, 6.9 Hz), 3.77−4.02 (3H, m), 3.76 (1H, dd, *J* = 8.2, 2.1 Hz), 2.21 (1H, dd, *J* = 13.7, 2.5 Hz), 2.10 (1H, dd, 1H, *J* = 13.8, 10.2 Hz), 1.21−1.72 (14H, m), 1.17 (12H, d, *J* = 6.6 Hz), 0.94 (3H, t, *J* = 6.9 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 154.67, 143.34, 139.87, 128.25, 127.85, 127.05, 114.97, 110.41, 82.04, 81.51, 74.50, 72.76, 67.52, 45.49−47.09, 43.13, 39.07, 36.89, 36.79, 25.11, 23.86, 20.01−21.75, 19.17, 14.14; mass spectrum (CI) *m*/*z* 518.4 ($M + H^+$, 7); HRMS calcd for for $C_{30}H_{47}NO_6$ (CI, $M + H^+$) 518.3481, found 518.3477.

***syn*-4-Hydroxy-2,6-dipropyl-tetrahydropyran-3-yl-diisopropylcarbamate (42).** A solution of tetrahydropyran **30** (709 mg, 2.181 mmol) in dichloromethane (15 mL) at −78 °C was treated with ozone until the solution turned blue. Dimethyl sulfide (481 μL, 6.545 mmol) was then added and the reaction mixture was allowed to warm slowly to room temperature and was then stirred for 18 h. The mixture was evaporated in vacuo to afford crude ketone **41**, which was used in the next step without further purification. To a solution of crude ketone **41** (100 mg, 0.284 mmol) in THF (5 mL) at −78 °C was added a 1 M solution of L-Selectride (341 μL, 0.341 mmol) in THF. The temperature was allowed to warm to 0 °C over 3 h. The reaction mixture was diluted with diethyl ether (20 mL) and poured onto saturated NH_4Cl (20 mL), and the aqueous layer was extracted with diethyl ether (2 × 20 mL). The combined organic layers were dried ($MgSO_4$), filtered, and evaporated in vacuo. The residue was purified by column chromatography (silica gel, petroleum ether/ethyl acetate 3/1) to give tetrahydropyran **42** as a colorless oil (69 mg, 74%). IR (neat) 3447, 1670, 1442 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.93 (1H, d, *J* = 3.0 Hz), 3.90−4.04 (2H, m), 3.90 (1H, ddd, *J* = 11.8, 5.0, 3.1 Hz), 3.36 (1H, dd, *J* = 7.2, 4.7 Hz), 3.25−3.36 (1H, m), 1.78 (1H, dddd, *J* = 12.6, 5.0, 2.0; 1.2 Hz), 1.32−1.72 (9H, m), 1.21−1.29 (12H, m), 0.92 (3H, t, *J* = 7.0 Hz), 0.91 (3H, t, *J* = 7.2 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 155.01, 76.87, 75.63, 72.92, 70.42, 46.04−46.48, 38.08, 35.50, 33.86, 20.63-21.52, 18.91, 18.77, 14.00, 13.95; mass spectrum (EI) *m*/*z* 329.2 ($M^{\bullet+}$, 22). Anal. Calcd for $C_{18}H_{35}NO_4$: C, 65.62; H, 10.71; N, 4.25. Found: C, 65.42; H, 10.66; N, 4.23.

***anti*-4-Hydroxy-2,6-dipropyl-tetrahydropyran-3-yl-diisopropylcarbamate (43).** IR (neat) 3439, 1668 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.54 (1H, dd, *J* = 3.0, 1.2 Hz), 4.04 (1H, q, *J* = 3.0 Hz), 3.82 (1H, ddd, *J* = 8.4, 4.5, 1.3 Hz), 3.80−4.05 (2H, m), 3.25−3.36 (1H, m), 3.66−3.75 (1H, m), 2.60 (1H, m), 1.30−1.64 (10H, m), 1.21 (12H, d, *J* = 6.6 Hz), 0.90 (3H, t, *J* = 6.8 Hz), 0.89 (3H, t, *J* = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.10, 73.12, 72.16, 71.33, 65.71, 45.50−46.48, 38.38, 34.42, 33.63, 20.52−21.51, 18.92, 18.75, 14.13, 14.06; mass spectrum (CI) *m*/*z* 330.2 ($M + H^+$, 100).

***syn*-2,6-Dipropyl-tetrahydropyran-3,4-diol (44). From carbamate 42:** To a solution of carbamate **42** (19 mg, 0.058 mmol) in THF (4 mL) was added a 1 M solution of $LiAlH_4$ (230 μL, 0.230 mmol) in diethyl ether. The reaction mixture was refluxed for 2 h, then diluted with dichloromethane (20 mL) and poured onto water (20 mL). The aqueous layer was extracted with dichloromethane (2 × 20 mL). The combined organic layers were dried ($MgSO_4$), filtered, and evaporated in vacuo. The residue was purified by column chromatography (silica gel, petroleum ether/ethyl acetate 1/2) to give diol **44** as a white solid (13 mg, 99%). IR (KBr) 3355 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.66 (1H, ddd *J* = 11.5, 5.2, 3.1 Hz), 3.61 (1H, d *J* = 3.2 Hz), 3.21−3.30 (2H, m), 2.07 (2H, br s), 1.81 (1H, dddd, *J* = 12.9, 5.2, 2.1, 0.9 Hz), 1.24−1.76 (9H, m), 0.93 (3H, t, *J* = 7.2 Hz), 0.90 (3H, t, *J* = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 77.99, 75.65, 70.26, 69.93, 37.91, 35.69, 33.35, 18.87, 13.96; mass spectrum (CI) *m*/*z* 203.1 ($M + H^+$, 13). Anal. Calcd for $C_{11}H_{22}O_3$: C, 65.31; H, 10.96. Found: C, 65.28; H, 10.86. **From tetrahydropyran 30:** Ozonolysis of **30** was performed as described above. To a solution of crude ketone **41** (50 mg, 0.122 mmol) in THF (8 mL) at 0 °C was added a 1 M solution of $LiAlH_4$ (488 μL, 0.480 mmol) in THF. The reaction mixture was stirred 10 min at 0 °C, refluxed 2 h, then diluted with diethyl ether (20 mL) and finally poured onto saturated NH_4Cl (20 mL). The aqueous layer was extracted with diethyl ether (2 × 20 mL). The combined organic layers were dried ($MgSO_4$), filtered, and evaporated in vacuo. The residue was purified by column chromatography (silica gel, petroleum ether/ethyl acetate 1/2) to give diol **44** as a white solid (24 mg, 98%).

4,6-Dipropyl-tetrahydro-[1,3,2]dioxathiolo[4,5-*c*]pyran-2,2-dioxide (49). To a solution of diol **44** (273 mg, 1.349 mmol) in CCl_4 (25 mL) was added thionyl chloride (118 μL, 1.619 mmol) and the reaction mixture was refluxed for 1 h. After cooling at 0 °C, the solution was diluted with acetonitrile (25 mL). $RuCl_3 \cdot xH_2O$ (6 mg, 0.027 mmol), $NaIO_4$ (433 mg, 2.024 mmol), and water (37 mL) were successively added and the solution was stirred at room temperature for 18 h. The reaction mixture was diluted with diethyl ether (50 mL) and water (20 mL). The organic layer was separated, washed with saturated $NaHCO_3$ (40 mL) and saturated NaCl (40 mL), dried ($MgSO_4$), filtered, and evaporated in vacuo to give cyclic sulfate **49** as a

colorless oil (321 mg, 90%). IR (neat) 2962, 2936, 2875, 1386, 1210, 1096, 975, 845, 739 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 5.00 (1H, ddd, J = 10.9, 7.0, 4.8 Hz), 4.80 (1H, dd J = 4.7, 1.6 Hz), 3.56 (1H, ddd, J = 8.4, 4.1, 1.5 Hz), 3.18−3.30 (1H, m), 2.18 (1H, ddd, J = 13.4, 7.0, 1.8 Hz), 1.90 (1H, td, J = 13.4, 10.5 Hz), 1.23−1.87 (8H, m), 0.94 (3H, t, J = 7.2 Hz), 0.90 (3H, t, J = 7.2 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 80.99, 80.06, 74.83, 73.59, 37.33, 33.31, 33.04, 18.56, 18.47, 13.70, 13.58; mass spectrum (EI) m/z 264.1 ($M^{\bullet+}$, 11). Anal. Calcd for $C_{11}H_{20}O_5S$: C, 49.98; H, 7.63; S, 12.13. Found: C, 50.18; H, 7.61; S, 11.60.

***anti*-2,6-Dipropyl-tetrahydropyran-3,4-diol (48).** To a solution of cyclic sulfate **49** (164 mg, 0.619 mmol) in DMF (15 mL) was added ammonium benzoate (173 mg, 1.238 mmol) and the reaction mixture was stirred at 130 °C for 18 h. After cooling at room temperature, the solution was diluted with dichloromethane (30 mL) and water (30 mL). The aqueous layer was extracted with dichloromethane (2 × 30 mL). The combined organic layers were dried ($MgSO_4$), filtered, and evaporated in vacuo to afford crude hydroxyester **50**, which was dissolved in MeOH (20 mL). NaOH (173 mg, 4.333 mmol) was then added and the reaction mixture was stirred at room temperature for 18 h. The solution was diluted with dichloromethane (30 mL) and poured onto a 1 N HCl solution (30 mL). The aqueous layer was extracted with dichloromethane (2 × 30 mL). The combined organic layers were dried ($MgSO_4$), filtered, and evaporated in vacuo. The residue was purified by column chromatography (silica gel, petroleum ether/ethyl acetate 1/1) to give diol **48** as a white solid (75 mg, 60%). IR (KBr) 3412 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.99 (1H, q, J = 3.0 Hz), 3.72 (1H, dd J = 8.5, 4.1 Hz), 3.62−3.69 (1H, m), 3.31 (1H, d, J = 3.3 Hz), 2.55−2.95 (2H, m), 1.23−1.73 (10H, m), 0.91 (3H, t, J = 7.1 Hz), 0.89 (3H, t, J = 7.1 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 74.34, 72.25, 70.10, 68.19, 38.11, 34.17, 33.11, 18.79, 18.66, 13.95, 13.91; mass spectrum (EI) m/z 203.3 (M + H^+, 7). HRMS calcd for for $C_{11}H_{23}O_3$ (CI, M + H^+) 203.1647, found 203.1649.

2-Trimethylsilylmethyl-allyl-[2-(*tert*-butyl-diphenyl-silyloxy)-ethyl]-isopropyl-carbamate (54). To a suspension of NaH (60% in mineral oil, 1.20 g, 30.0 mmol) in diethyl ether (20 mL) at 0 °C was added a solution of alcohol **12** (2.88 g, 20.0 mmol) in diethyl ether (20 mL). After the mixture was stirred for 15 min at room temperature, a solution of diisopropylcarbamoyl chloride (8.08 g, 20.0 mmol) in diethyl ether (20 mL) was added and the solution was stirred at rom temperature for 18 h. The mixture was poured onto saturated aqueous NH_4Cl (40 mL) and extracted with dichloromethane (2 × 40 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography over silica gel (petroleum ether/ethyl acetate 40/1) to give **54** as a colorless oil (7.30 g, 71%). IR (neat) 1703, 1644 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 50 °C) δ 7.66−7.70 (4H, m), 7.26−7.45 (6H, m), 4.83 (1H, s), 4.67 (1H, s), 4.41 (2H, s), 4.19 (1H, hept, J = 7.0 Hz), 3.77 (2H, t, J = 7.0 Hz), 3.33 (2H, t, J = 7.1 Hz), 1.51 (2H, s), 1.06−1.09 (6H, m), 1.07 (9H, s), 0.04 (9H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 155.70, 142.49, 135.56, 133.73, 129.64, 127.67, 108.45, 68.27, 62.75 (br), 47.85, 44.55 (br), 26.90, 23.53, 20.65 (br), 19.19, −1.42; mass spectrum (EI) m/z 511.3 ($M^{\bullet+}$, 8). Anal. Calcd for $C_{29}H_{45}NO_3Si_2$: C, 68.05; H, 8.86; N, 2.74. Found: C, 67.72; H, 8.84; N, 2.73.

2-Trimethylsilylmethyl-allyl-[2-(*tert*-butyl-diphenyl-silyloxy)-ethyl]-isopropyl-carbamate (55). To a solution of TMEDA (59 μL, 0.392 mmol) in diethyl ether (1 mL) at −78 °C was added *n*-BuLi (1.6 M solution in hexane, 245 μL, 0.392 mmol) and the resulting solution was stirred for 30 min at −78 °C. A solution of allylcarbamate **54** (100 mg, 0.196 mmol) in diethyl ether (1 mL) was added dropwise and the solution was stirred for 30 min at −78 °C. Titanium tetraisopropoxide (173 μL, 0.588 mmol) was added in one portion and the solution was stirred for 30 min at −78 °C. A solution of butyraldehyde (22 mg, 0.294 mmol) in diethyl ether (1 mL) was quickly added and the temperature was allowed to warm to 0 °C by changing the dry ice/acetone bath for an ice bath immediatly after the addition of the aldehyde. After stirring 15 min at 0 °C, the reaction mixture was diluted with diethyl ether (20 mL) and poured onto 1 N HCl (20 mL). The organic layer was separated and washed with saturated $NaHCO_3$ (20 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography over silica gel (petroleum ether/ethyl acetate 8/1) to give **55** as a colorless oil (58 mg, 51%). IR (neat) 3483, 1709 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.66 (4H, dd, J = 7.5, 1.6 Hz), 7.36−7.44 (6H, m), 6.76 (1H, s), 4.09−4.18 (1H, m), 3.66−3.77 (3H, m), 3.22−3.35 (2H, m), 2.30 (1H, dd, J = 13.5, 8.8 Hz), 1.94−2.12 (1H, m), 1.22−1.73 (6H, m), 0.84−1.09 (9H, m), 1.05 (9H, s), 0.03 (9H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 153.63, 135.58, 133.57, 131.77, 129.72, 127.72, 118.74, 69.31, 62.75 (br), 48.14, 44.52 (br), 39.54, 36.65, 26.89, 21.04, 20.35, 19.17, 18.93, 14.07, −1.19; mass spectrum (EI) m/z 583.4 ($M^{\bullet+}$, 2). Anal. Calcd for $C_{33}H_{53}NO_4Si_2$: C, 67.88; H, 9.15; N, 2.40. Found: C, 67.84; H, 9.13; N, 2.29.

4-Methylene-2,6-dipropyl-tetrahydropyran-3-yl-[2-(*tert*-butyl-diphenyl-silyloxy)-ethyl]-isopropylcarbamate (56). To a solution of homoallylic alcohol **55** (629 mg, 1.078 mmol) and butyraldehyde (86 mg, 1.186 mmol) in dichloromethane (12 mL) at −78 °C was added slowly $BF_3{\cdot}Et_2O$ (146 μL, 1.186 mmol). The temperature was allowed to warm to 0 °C over 3 h. The reaction mixture was poured onto saturated $NaHCO_3$ (25 mL) and the aqueous layer was extracted with dichloromethane (2 × 25 mL). The combined organic layers were dried ($MgSO_4$), filtered, and evaporated in vacuo. The residue was purified by column chromatography (silica gel, petroleum ether/ethyl acetate 10/1) to give tetrahydropyran **56** as a colorless oil (509 mg, 84%). IR (neat) 1700, 1657 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 50 °C) δ 7.63−7.68 (4H, m), 7.32−7.40 (6H, m), 5.06 (1H, br s), 5.03 (1H, d, J = 1.1 Hz), 4.86 (1H, br s), 4.03−4.23 (1H, m), 3.72−3.77 (2H, m), 3.18−3.40 (4H, m), 2.02−2.13 (2H, m), 1.29−1.58 (8H, m), 1.05−1.06 (15H, m), 0.89 (3H, t, J = 6.5 Hz), 0.88 (3H, t, J = 7.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, 40 °C) δ 155.63, 143.24, 135.55, 133.77, 129.57, 127.64, 113.08 (br), 79.84, 78.36, 74.51, 62.90 (br), 47.88, 45.02 (br), 38.38, 37.44, 33.66, 26.67, 20.74 (br), 19.18, 18.88, 18.71, 13.94; mass spectrum (EI) m/z 565.7 ($M^{\bullet+}$, 2). Anal. Calcd for $C_{34}H_{51}NO_4Si$: C, 72.17; H, 9.08; N, 2.48. Found: C, 72.20; H, 9.16; N, 2.48.

4-Methylene-2,6-dipropyl-tetrahydropyran-3-ol (46). To a solution of carbamate **56** (150 mg, 0.265 mmol) in methanol (6 mL) was added $LiOH{\cdot}1H_2O$ (279 mg, 6.637 mmol). The reaction mixture was refluxed for 4 h, then diluted with dichloromethane (25 mL) and poured onto 1 N HCl solution (20 mL). The aqueous layer was extracted with dichloromethane (2 × 25 mL). The combined organic layers were dried ($MgSO_4$), filtered, and evaporated in vacuo. The residue was purified by column chromatography (silica gel, petroleum ether/ethyl acetate 8/1) to give tetrahydropyran **46** as a colorless oil (49 mg, 94%). IR (neat) 3440, 1655 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.93 (1H, t, J = 1.7 Hz), 4.81 (1H, t, J = 1.9 Hz), 3.84 (1H, d, J = 7.4 Hz), 3.24−3.32 (2H, m), 2.26 (1H, tt, J = 13.7, 1.9 Hz), 2.18 (1H, dd, J = 13.7, 2.7 Hz), 2.06 (1H, d, J = 7.6 Hz), 1.25−1.78 (8H, m), 0.94 (3H, t, J = 7.2 Hz), 0.92 (3H, t, J = 7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.61, 110.52, 80.73, 78.64, 72.92, 38.22, 36.42, 33.25, 18.85, 18.76, 14.02, 13.97; mass spectrum (EI) m/z 199.0 (M + H^+, 57).

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Supporting Information Available: Full characterization data for compounds **20**, **21**, **22**, **23**, **24**, **25**, **26**, **31**, **32**, **33**, and **34**. This material is available free of charge via the Internet at http://pubs.acs.org.

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