Synthesis of Enantio- and Diastereomerically Pure, Tetra- and Penta-Substituted Cyclopentanes by the Desymmetrization of *endo*-Norborn-5-ene-2,3-dicarboxylic Anhydrides

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The desymmetrization of *endo*-norborn-5-ene-2,3-dicarboxylic anhydrides by methyl (*S*)-prolinate followed by ozonolysis of the resulting carboxylic acids is used to prepare enantio- and diastereomerically pure, tetra- and penta-substituted cyclopentane derivatives in which all of the substituents on the cyclopentane ring are syn to one another. The initial products of this chemistry (**2a**,**b** and **18a**,**b**) contain two aldehyde groups, one of which exists as a hemiacetal. This allows subsequent chemistry to be carried out regioselectively at one of the two aldehyde groups. Hence, the sodium borohydride reduction of hemiacetals **2a**,**b** can be controlled to give either a bicyclo[3.2.1] (**4**) or bicyclo[3.3.0] lactone (**5**) as the product. The addition of allylindium to hemiacetals **2a**,**b** occurs both regio- and diastereoselectively to give polycyclic acetal **12**, the stereochemistry of which is consistent with a chelation controlled addition. It is possible to remove the proline ester based auxiliary from the cyclopentane derivatives by γ-lactone formation under mild reaction conditions.

Introduction

The desymmetrization of an achiral meso compound by reaction with a suitable enantiomerically pure reagent provides a versatile approach to the preparation of enantiomerically pure starting materials for asymmetric synthesis.[1] The most common classes of chemicals which can be subjected to desymmetrization include diols, diesters, and anhydrides. In the latter case, both chiral alcohols and chiral amines can be used to generate stereochemically pure products containing two different functional groups: an acid and either an ester or an amide. In recent publications,[2] we have shown that esters of the naturally occurring, enantiomerically pure amino acid (*S*)-proline can be used to desymmetrize a wide range of meso anhydrides, forming amido acids with high diastereomeric excesses. The applications of this chemistry to date have focused upon the synthesis of conformationally constrained peptide analogues where the proline unit is retained within the final product.[3] In this paper, however, the conversion of the enantio- and diastereomerically pure amido acid **1**, which is easily obtained from methyl (*S*)-prolinate and *endo*-norborn-5-ene-2,3-dicarboxylic anhydride, into enantiomerically pure cyclopentane derivatives is reported.[4]

Highly substituted cyclopentane rings are found within many biologically active natural and unnatural products such as prostaglandins, carbocyclic nucleosides, and carba-sugars. Specific examples include (+)-mannostatin A which inhibits Golgi from processing mannosidase II, sarkomycin an antibiotic, (−)-aristeromycin an antineoplasic antibiotic, and trehazolin an inhibitor of the enzyme trehalase which is involved in the control of insects and certain fungi.[5] The stereocontrolled synthesis of cyclopentane derivatives is, however, more challenging

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(1) Wong, C.-H.; Whitesides, G. M. *Enzymes in Synthetic Organic Chemistry*; Pergamon: London, 1994; pp 143−8. Lok, K. P.; Jakovac, I. J.; Jones, J. B. *J. Am. Chem. Soc.* **1985**, *107*, 2521. Metz, P. *Tetrahedron* **1989**, *45*, 7311. Harada, T.; Wada, I.; Oku, A. *J. Org. Chem.* **1989**, *54*, 2599. Ward, R. S. *Chem. Soc. Rev.* **1990**, *19*, 1. Romagnoli, R.; Roos, E. C.; Hiemstra, H.; Moolenaar, M. J.; Speckamp, W. N.; Kaptei, B.; Schoemaker, H. E. *Tetrahedron Lett.* **1994**, *35*, 1087. Hatakeyama, S.; Sakurai, K.; Takano, S. *J. Chem. Soc., Chem. Commun.* **1985**, 1759. Partridge, J. J.; Chadha, N. K.; Uskokovic, M. R. *J. Am. Chem. Soc.* **1973**, *95*, 532. Kawakami, Y.; Hiratake, J.; Yamamoto Y.; Oda, J. *J. Chem. Soc., Chem. Commun.* **1984**, 779. Ward, R. S.; Pelter, A.; Edwards, M. I.; Gilmore J. *Tetrahedron: Asymmetry* **1995**, *6*, 843. Rosen, T.; Heathcock, C. H. *J. Am. Chem. Soc.* **1985**, *107*, 3731. Theisen, P. D.; Heathcock, C. H. *J. Org. Chem.* **1993**, *58*, 142. Hashimoto, N.; Kawamura, S.; Ishizuka, T.; Kunieda, T. *Tetrahedron Lett.* **1996**, *37*, 9237. Imado, H.; Ishizuka, T.; Kunieda, T. *Tetrahedron Lett.* **1995**, *36*, 931. Hiratake, J.; Inagaki, M.; Yamamoto, Y.; Oda, J. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1053. Aitken, R. A.; Gopal, J.; Hirst, J. A. *J. Chem. Soc., Chem. Commun.* **1988**, 632. Aitken, R. A.; Gopal, J. *Tetrahedron: Asymmetry* **1990**, *1*, 517. Shimizu, M.; Matsukawa, K.; Fujisawa, T. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 2128. Seebach, D.; Jaeschke, G.; Wang, Y. M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2395. Jaeschke, G.; Seebach, D. *J. Org. Chem.* **1998**, *63*, 1190. Real, S. D.; Kronenthal, D. R.; Wu, H. Y. *Tetrahedron Lett.* **1993**, *34*, 8063. Matsuki, K.; Inoue, H.; Takeda, M. *Tetrahedron Lett.* **1993**, *34*, 1167. Osakada, K.; Obana, M.; Ikariya, T.; Saburi, M.; Yoshikawa, S. *Tetrahedron Lett.* **1981**, *22*, 4297. Ohtani, M.; Matsuura, T.; Watanabe, F.; Narisada, M. *J. Org Chem.* **1991**, *56*, 4120. Mukaiyama, T.; Yamashita, H.; Asami, M. *Chem. Lett.* **1983**, 385. Suda, Y.; Yago, S.; Shiro, M.; Taguchi, T. *Chem. Lett.* **1992**, 389. Ohshima, M.; Mukaiyama, T. *Chem. Lett.* **1987**, 377. Das, J.; Haslanger, M. F.; Gougoutas, J. Z.; Malley, M. F. *Synthesis* **1987**, 1100.

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(3) Jones, I. G.; Jones, W.; North, M. *Synlett* **1997**, 63. Jones, I. G.; North, M. *Lett. Peptide Sci.* **1998**, *5*, 171. Hibbs, D. E.; Hursthouse, M. B.; Jones, I. G.; Jones, W.; Malik, K. M. A.; North, M. *J. Org. Chem.* **1998**, *63*, 1496. Jones, I. G.; Jones, W.; North, M. *J. Org. Chem.* **1998**, *63*, 1505. Hibbs, D. E.; Hursthouse, M. B.; Jones, I. G.; Jones, W.; Malik, K. M. A.; North, M. *Tetrahedron* **1997**, *53*, 17417. Jones, I. G.; Jones, W.; North, M. *Tetrahedron* **1999**, *55*, 279.

(4) For a preliminary account of some of this work, see: Jones, I. G.; Jones, W.; North, M. *Synlett* **1997**, 1478.

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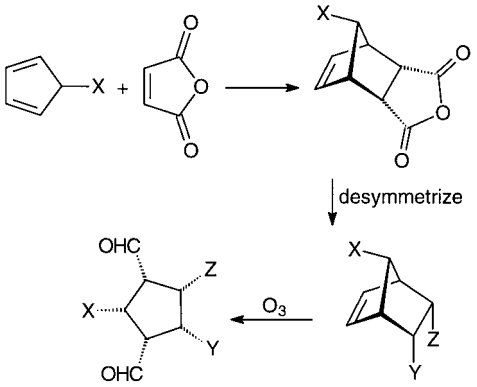
Scheme 1

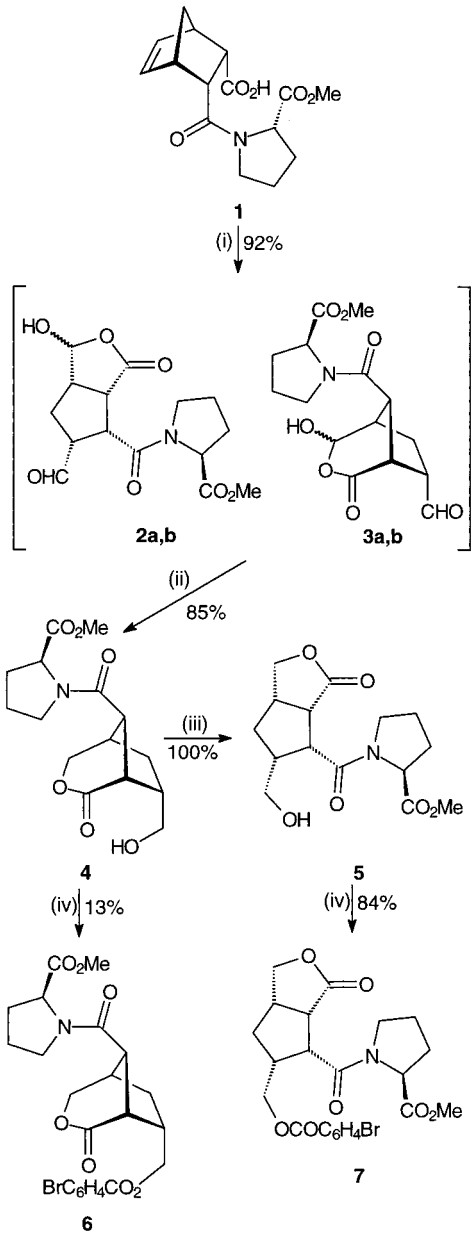


than the synthesis of cyclohexane derivatives since most five-membered ring containing compounds do not have a single, low-energy conformation.[6] This is in contrast to the situation with cyclohexane derivatives where often, the desire for the six-membered ring to adopt a chair conformation and for substituents attached to the ring to adopt equatorial positions results in only one conformation having a significant population.[7] An attractive solution to this problem is to use a conformationally rigid norbornene derivative as a cyclopentane precursor. This approach is particularly appealing given the ease with which diastereomerically pure norbornene derivatives bearing substituents at the 2, 3, and 7 positions can be prepared by Diels−Alder reactions.[8] Oxidative cleavage of the alkene bond within the norbornene would then reveal a cyclopentane ring bearing two aldehyde substituents and with substituents on the remaining carbon atoms if desired. The aldehyde groups provide sites for further manipulation, provided that they can be distinguished. In this manuscript, we show how the combination of a Diels−Alder reaction between cyclopentadiene derivatives and maleic anhydride, followed by desymmetrization and ozonolysis can be used in an enantio- and diastereocontrolled synthesis of highly substituted cyclopentanes as outlined in Scheme 1.

Results

Reaction of *endo*-norborn-5-ene-2,3-dicarboxylic anhydride with methyl (*S*)-prolinate gave amido acid **1** as a single stereoisomer as previously reported.[2] Gratifyingly, ozonolysis of amido acid **1** proceeded in 92% yield to give a 1:1 mixture of two products which were identified as either the epimeric [3.3.0]bicyclic aldehydes **2a**,**b**, or the corresponding [3.2.1]bicyclic aldehydes **3a**,**b** as shown in Scheme 2. It has not proven possible to unambiguously assign structures to these two compounds, but on the basis of subsequent results and the fact that molecular

Scheme 2[a]



[a] Reagents: (i) O_3 then Me_2S; (ii) $NaBH_4$/MeOH; (iii) $CHCl_3$ or *p*-$TolSO_3H$; (iv) BrC_6H_4COCl/Et_3N.

mechanics calculations suggested that [3.3.0]bicyclic systems are thermodynamically more stable than the corresponding [3.2.1]bicyclic compounds, the compounds have been tentatively assigned structures **2a**,**b**. Notably however, whichever aldehydes were formed, one of the two aldehydes generated during the ozonolysis was converted into a hemiacetal, and it was envisaged that this would allow subsequent chemistry to be carried out selectively on one of the aldehydes.

To obtain a compound which could be unambiguously identified, the mixture of aldehydes **2a**,**b** was treated with sodium borohydride. This resulted in the reduction of both the aldehyde and hemiacetal functionalities, giving [3.2.1]bicyclic lactone **4** as the initial product. On standing in $CHCl_3$, or more quickly on treatment with *p*-toluenesulfonic acid, lactone **4** isomerized to the corresponding [3.3.0]bicyclic lactone **5**. ^1H and ^{13}C NMR spectroscopy could not distinguish between the [3.2.1]

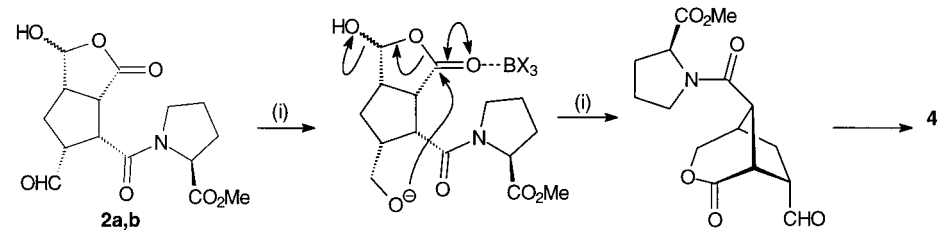
(5) For selected examples, see: Tropea, J. E.; Kaushal, G. P.; Pastuszak, I.; Mitchell, M.; Aoyagi, T.; Molyneux, R. J.; Elbein, A. D. *Biochemistry* **1990**, *29*, 10062. Aoyagi, T.; Yamamoto, T.; Kojiri, K.; Morisha, H.; Nagai, M.; Hamada, M.; Takeuchi, T.; Umezawa, H. *J. Antibiot.* **1989**, *42*, 883. Scarborough, R. M., Jr.; Toder, B. H.; Smith, A. B., III *J. Am. Chem. Soc.* **1980**, *102*, 3904. Altmann, K.-H.; Kesselring, R.; Francotte, E.; Rihs, G. *Tetrahedron Lett.* **1994**, *35*, 2331. Ando, O.; Satake, H.; Itoi, K.; Sato, A.; Nakajima, M.; Takahashi, S.; Haruyama, H. *J. Antibiot.* **1991**, *44*, 1165.

(6) Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; Wiley: New York, 1994; pp 758−62.

(7) Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; Wiley: New York, 1994; pp 686−754.

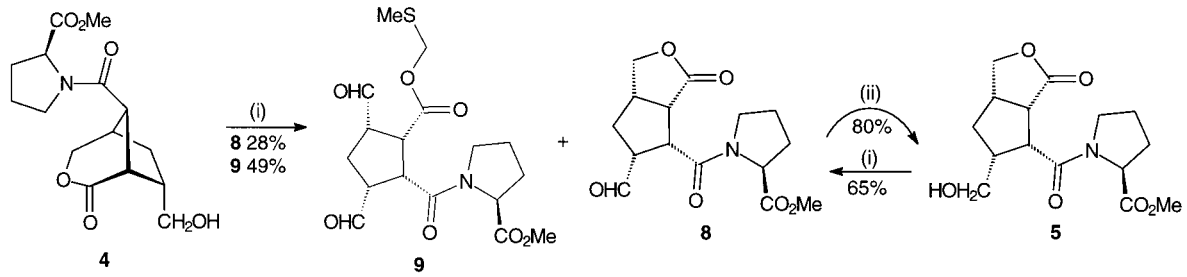
(8) For a review and leading reference see: March, J. *Advanced Organic Chemistry* 4th ed.; Wiley: New York, 1992; pp 839−46.

Scheme 3[a]



[a] Reagents: (i) $NaBH_4$.

Scheme 4[a]

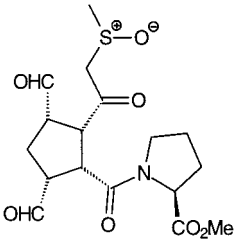


[a] Reagents: (i) $Me_2SO/Et_3N/ClCOCOCl$; (ii) $NaBH_4$.

and [3.3.0]bicyclic structures in lactones **4** and **5**; however, the structures of these lactones were unambiguously determined by X-ray crystallography. Crystals of lactone **5** suitable for X-ray analysis could be obtained. Lactone **4** however, did not form crystals suitable for X-ray analysis, so it was converted to the corresponding *p*-bromobenzoate **6** (yield not optimized) which was suitable for X-ray analysis. To prove that no isomerism between the [3.2.1] and [3.3.0]bicyclic ring systems occurred under the esterification conditions, lactone **5** was also converted into *p*-bromobenzoate **7**. No contamination of compound **7** with compound **6** or vice versa was detected in these reactions. In addition to showing which bicyclic ring system was present in each of lactones **4** and **5**, the X-ray structures also confirmed that no epimerization of any of the stereocenters in compounds **4** or **5** had occurred during the ozonolysis or reduction processes.

An explanation for the initial formation of the strained [3.2.1]bicyclic lactone **4** is shown in Scheme 3. Thus, the hemiacetal of compounds **2a**,**b** acts as a partial protecting group for one of the aldehydes, and sodium borohydride then preferentially reduces the other aldehyde. Cyclization of the resulting alkoxide (probably assisted by a Lewis acid generated *in situ* from the sodium borohydride) generates the [3.2.1]bicyclic ring system, and simultaneously deprotects the other aldehyde, which is then reduced to an alcohol after formation of the bicyclic ring system. Whatever the mechanism of this transformation, it is possible to isolate either lactone **4** or lactone **5** from the reduction, and both compounds contain a cyclopentane ring with four different substituents all oriented syn to one another.

Having demonstrated that it was possible to prepare diastereomerically pure lactones **4** and **5**, the oxidation of the alcohol functionality in these compounds to the corresponding aldehyde was investigated. It was anticipated that this oxidation would both prevent the isomerization of the [3.2.1]ring system to the thermodynamically more stable [3.3.0]isomer, and provide a site for subsequent stereoselective nucleophilic addition reactions. The oxidation of lactone **5** proceeded without difficulty under standard Swern oxidation[9] conditions to give aldehyde **8** (Scheme 4). That no rearrangement occurred during the oxidation reaction was shown by reduction of aldehyde **8** back to alcohol **5**. In contrast, however, oxidation of lactone **4** gave none of the expected aldehyde attached to a [3.2.1]bicyclic ring system. The major product of this reaction was identified as the methylthiomethyl ester containing cyclopentane dicarboxaldehyde derivative **9**, which was always accompanied by about 30% of aldehyde **8**, the latter presumably being formed by the rearrangement of lactone **4** to lactone **5** under the acidic reaction conditions. The structure of compound **9** was determined to be the methylthiomethyl ester rather than the isomeric β-ketosulfoxide **10** on the basis of the ^1H NMR chemical shifts of the diastereotopic SCH_2O protons,[10] the absence of a ketone carbonyl in the ^{13}C NMR spectrum, and the absence of a sulfoxide stretch in the infrared spectrum.

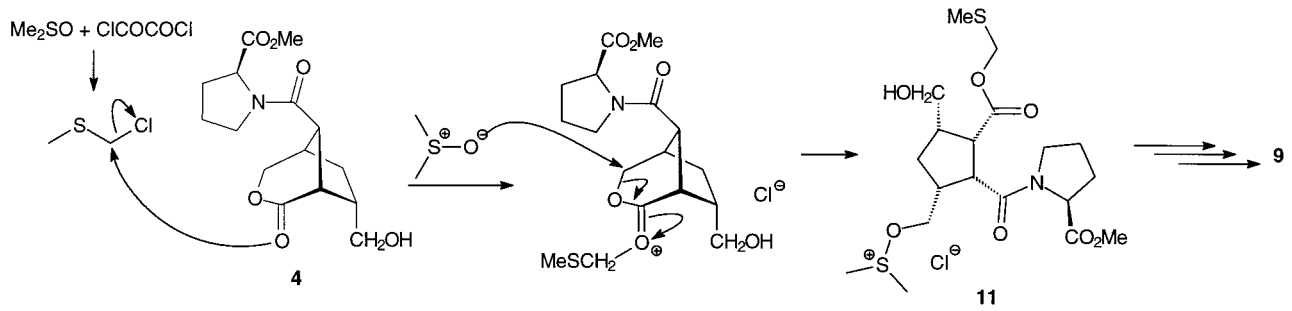


The unexpected formation of dialdehyde **9** can be explained by a Pummerer rearrangement as shown in Scheme 5. Thus, initial reaction between oxalyl chloride and DMSO generates chloromethyl methylthioether,[11] which can alkylate the lactone carbonyl. This alkylation

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

(10) For a previous report of the ^1H NMR chemical shifts of a methylthiomethyl ester, see: Kukla, M. J. *Tetrahedron Lett.* **1982**, *23*, 4539. For the ^1H NMR chemical shifts of a β-ketosulfoxide, see: Drewe, J. A.; Groundwater, P. W. *J. Chem. Soc., Perkin Trans. 1* **1997**, 601.

Scheme 5

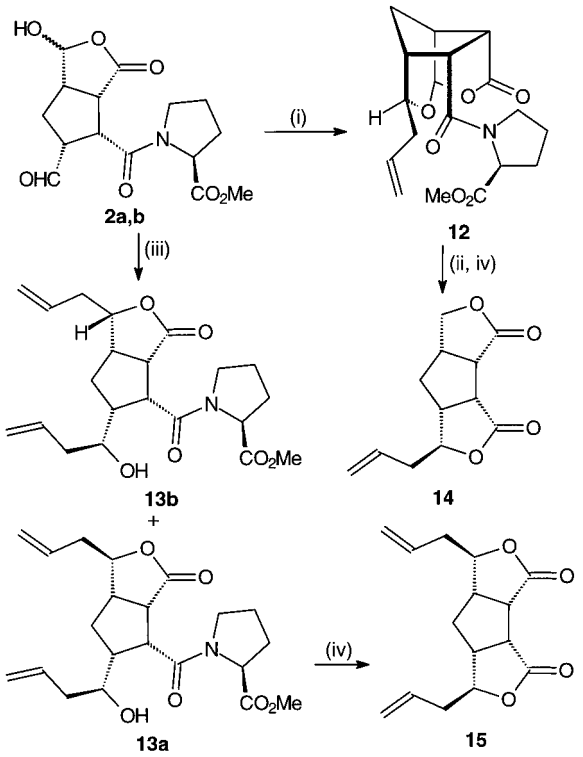


is likely to be assisted by the strain in the [3.2.1]ring system. Subsequent lactone ring opening by DMSO leads to an intermediate **11** in which the methylthiomethyl ester has been formed, and one of the two alcohols has been converted into an intermediate which forms during a Swern oxidation. From intermediate **11**, compound **9** can be formed by standard Swern oxidations. The formation of dialdehyde **9** requires 3 equiv of DMSO, and Swern oxidations are normally carried out using a 3-fold excess of DMSO. The oxidation of lactone **4** was also attempted using a stoichiometric amount of DMSO, but this resulted in a reduced yield of dialdehyde **9** and the isolation of lactone **5** as the only products.

In view of these results, it appeared unlikely that the asymmetric addition of nucleophiles to aldehydes derived from lactones **4** or **5** would provide a viable route to highly substituted cyclopentanes. However, compounds **2a**,**b** contain both a free aldehyde and an aldehyde which has been partially protected by conversion to a hemiacetal unit. It was apparent that if nucleophiles could be stereoselectively added to just the free aldehyde of compounds **2a**,**b**, then a short and highly versatile cyclopentane synthesis would be achieved. In the event, the reaction between compounds **2a**,**b** and Grignard or organolithium reagents was not encouraging, with complex mixtures of products being obtained. The results reported by Paquette *et al.*[12] on the addition of allylindium reagents to aldehydes in aqueous solvent systems[13] appeared to offer considerable potential for application to our system. In particular, Bernadelli and Paquette have reported the diastereoselective addition of allylindium to γ-hydroxy-γ-lactones.[14] The reaction of compounds **2a**,**b** with 1 equiv of allylindium in an ethanol/water mixture gave a single isolated product, which on the basis of its spectra was assigned as acetal **12** (Scheme 6), though the configuration of the newly created stereocenter was not clear at this stage. The addition of 2 equiv of allylindium to compounds **2a**,**b** gave a diallylated product **13a**,**b**, as a 4:1 ratio of diastereomers which were separable by chromatography.

Having found conditions for the diastereoselective addition of allylindium to compounds **2a**,**b**, it was desirable to determine the absolute configuration of compounds **12** and **13**, and to find a way of removing the proline based auxiliary. In the event, both aims were achieved by acid catalyzed lactonization. Thus, treatment of acetal **12** with sodium borohydride followed by *p*-toluenesulfonic acid resulted in reductive cleavage of the acetal unit followed by lactonization to allyl-bis-lactone **14** which was isolated as a single stereoisomer in 94% yield. Compound **14** was crystalline, and gave crystals suitable for X-ray analysis, which confirmed that the stereocenter adjacent to the allyl group had the (*S*)-configuration. It is notable that compound **14** which contains five contiguous stereocenters and functionality suitable for further manipulation can be prepared in a completely enantio- and diastereo controlled manner in just four steps from achiral *endo*-norborn-5-ene-2,3-dicarboxylic anhydride. The structure of the major diastereomer of alcohol **13** was also determined by treatment with *p*-toluenesulfonic acid to give the achiral meso compound **15**. The structure of bis-lactone **15** was apparent from the symmetry evident in its NMR spectra and its lack of optical activity.

Scheme 6[a]



[a] Reagents: (i) In (1.1 equiv), $H_2C{=}CHCH_2Br$ (1.5 equiv)/HCl/EtOH; (ii) $NaBH_4$; (iii) In (2.1 equiv), $H_2C{=}CHCH_2Br$ (2.5 equiv)/HCl/EtOH; (iv) *p*-$TolSO_3H$.

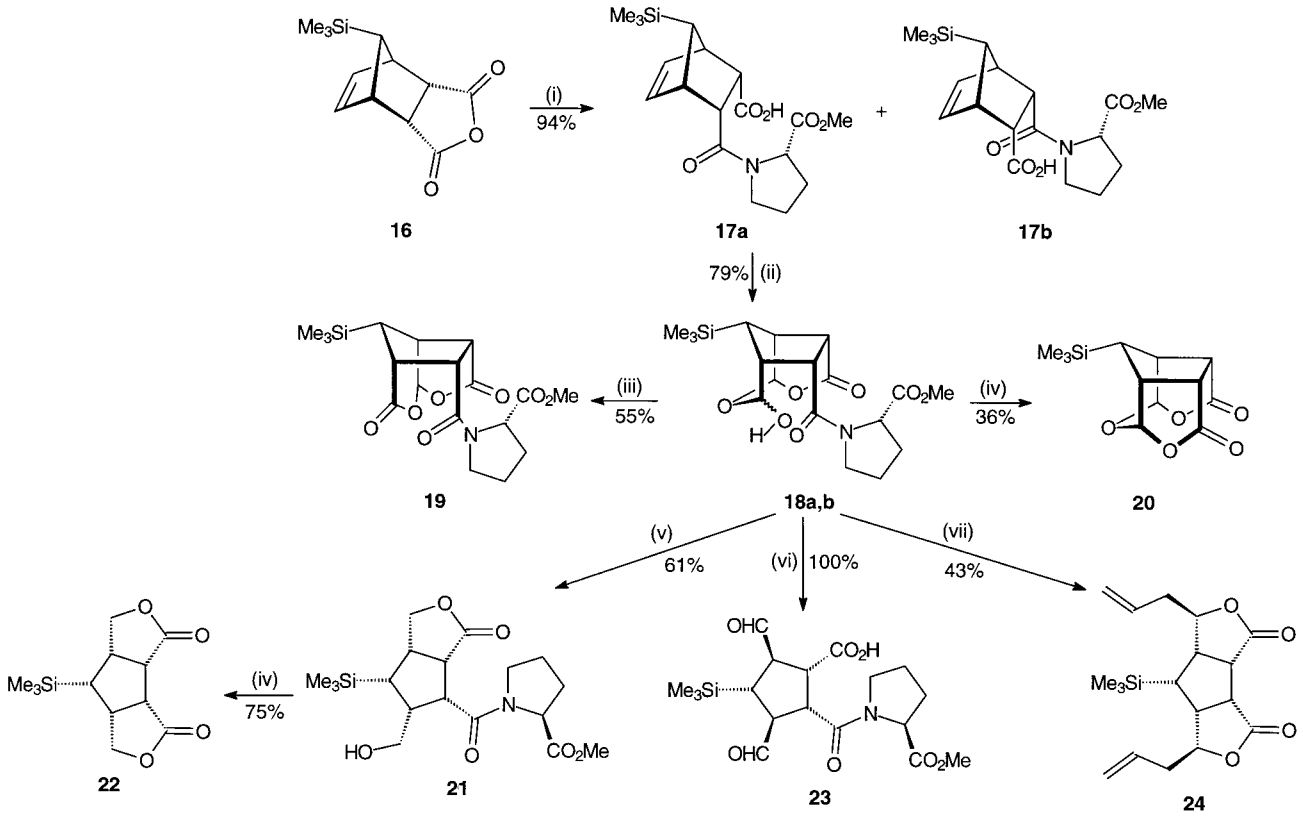
(11) There is literature precedent for the conversion of DMSO into chloromethyl methylthioether upon treatment with acid chlorides: Bordwell, F. G.; Pitt, B. M. *J. Am. Chem. Soc.* **1955**, *77*, 572. Amonoo-Neizer, E. H.; Ray, S. R.; Shaw, R. A.; Smith, B. C. *J. Chem. Soc.* **1965**, 6250. Thea, S.; Cevasco, G. *J. Org. Chem.* **1988**, *53*, 4121.

(12) Paquette, L. A.; Lobben, P. C. *J. Am. Chem. Soc.* **1996**, *118*, 1917. Paquette, L. A.; Mitzel, T. M. *J. Am. Chem. Soc.* **1996**, *118*, 1931. Paquette, L. A.; Mitzel, T. M.; Isaac, M. B.; Crasto, C. F.; Schomer, W. W. *J. Org. Chem.* **1997**, *62*, 4293. Isaac, M. B.; Paquette, L. A. *J. Org. Chem.* **1997**, *62*, 5333.

(13) For reviews on the use of organometallic reagents including organoindium reagents in aqueous solvent systems, see: Chan, T. H.; Li, C.-J.; Lee, M. C.; Wei, Z. Y. *Can. J. Chem.* **1994**, *72*, 1181. Li, C.-J. *Tetrahedron* **1996**, *52*, 5643.

(14) Bernadelli, P.; Paquette, L. A. *J. Org. Chem.* **1997**, *62*, 8284.

Scheme 7[a]



[a] Reagents: (i) HCl, (*S*)-Pro-OMe/Et_3N; (ii) O_3/MeOH then Me_2S; (iii) Me_2SO/ClCOCOCl/Et_3N; (iv) *p*-$TolSO_3H$; (v) $NaBH_4$; (vi) K_2CO_3; (vii) In (1.1 equiv)/$H_2C{=}CHCH_2Br$ (1.5 equiv)/HCl/THF.

The origin of the asymmetric induction in the formation of allyl adducts **12** and **13** can be explained by a chelation controlled addition of an allyl anion equivalent to the *si*-face of the aldehyde as shown in Figure 1. Thus, the indium ion complexes to both the aldehyde and amide oxygen atoms, and the cyclic hemiacetal unit blocks the *re*-face of the coordinated aldehyde. The allyl group may be transferred intra- or intermolecularly. During the addition of the second allyl group, a chelate involving the aldehyde and either the acid or amide carbonyls may be formed. The lower asymmetric induction observed during this addition is consistent with the lack of a rigid, cyclic group to block one face (the *si*-face) of the aldehyde.

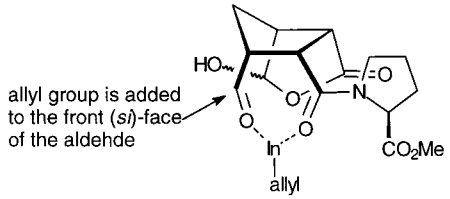


Figure 1. Structure of the chelated complex that accounts for the asymmetric induction during the addition of allylindium to hemiacetals **2a**,**b**.

Having shown that tetrasubstituted cyclopentane derivatives could be prepared using this methodology, it was of interest to investigate whether the same methodology could be used to prepare pentasubstituted cyclopentanes in which all five substituents are syn to one another. Trimethylsilyl was chosen as the fifth substituent since the required anhydride **16** is known[15] and can readily be prepared from 5-trimethylsilylcyclopentadiene[16] and maleic anhydride, silyl groups can be transformed into a wide range of other functionalities,[17] and the large size of the trimethylsilyl group was expected to provide a stringent test of the scope of the methodology. Desymmetrization of anhydride **16** by methyl (*S*)-prolinate gave a 3:1 ratio of diastereomeric acids **17a**,**b** (Scheme 7). The major isomer is assumed to have structure **17a**, based on precedent from all other *endo*-norbornane derived anhydrides previously investigated in this reaction.[2] The two diastereomeric acids **17a**,**b** were not readily separated; however, ozonolysis of the mixture followed by flash chromatography to remove products arising from diastereomer **17b**, gave a product which existed as a pair of epimers **18a**,**b**. Although compounds **18a**,**b** were clearly hemiacetals, no aldehyde group was evident in the ^1H or ^{13}C NMR spectra of the compound. However, additional low-field doublets were present in both the ^1H (5.8 and 5.9 ppm) and ^{13}C (99.5 and 102.8 ppm) spectra, and on this basis, the compounds are assigned the structure shown in Scheme 7 consisting of

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a fused tricyclic ring system containing both acetal and hemiacetal functionalities.

The tricyclic acetal−hemiacetal unit present in compounds **18a**,**b** appears to be remarkably stable, since Swern oxidation of compounds **18a**,**b** preserves the ring system and forms bis-lactone **19**. Even more remarkably, treatment of epimers **18a**,**b** with *p*-toluenesulfonic acid resulted in lactonization to give the achiral, tetracyclic bis-lactone **20**. Compound **20** has a very interesting structure in which the top face of the molecule is completely devoid of functionality, while the lower face contains five rigidly located oxygen atoms. The potential of this and similar compounds to act as metal ion complexing agents is currently under investigation.

Sodium borohydride reduction of hemiacetals **18a**,**b** produced lactone **21** which contains a [3.3.0]bicyclic ring system and is analogous to lactone **5** produced from the non-silylated hemiacetals **2a**,**b**. The presence of the corresponding [3.2.1]ring system was not observed in this case. Treatment of compound **21** with *p*-toluenesulfonic acid gave bis-lactone **22**. When hemiacetals **18a**,**b** were treated with even mild base (potassium carbonate), inversion of configuration at two of the five stereocenters on the cyclopentane ring occurred to give dialdehyde **23**. The stereochemistry of compound **23** was deduced from the fact that the ^{1}H and ^{13}C NMR spectra show that two aldehydes are present which implies that these are both anti to the acid group or hemiacetal formation would have been observed. This simple isomerization process opens the possibility of preparing highly substituted cyclopentanes with different stereochemical relationships between the substituents using this methodology.

Finally, the addition of allylindium to hemiacetals **18a**,**b** was investigated with the hope of producing a monoadduct analogous to compound **12**. However, under the conditions developed for the addition of allylindium to hemiacetals **2a**,**b**, no reaction occurred. Changing the organic cosolvent from ethanol to THF to better accommodate the more hydrophobic substrate did result in reaction, but bis-lactone **24** was the only allylated product isolated from this reaction, with tetracyclic bis-lactone **20** also being formed. It appears that the acid catalyzed lactonization of hemiacetals **18a**,**b** to bis-lactone **20** is so facile that it competes with the intermolecular addition of allylindium to hemiacetals **18a**,**b** under the reaction conditions. In an attempt to avoid the competing lactonization, the allylindium addition reaction was carried out in acetic acid/THF or water/THF mixtures, but no product was obtained from these reactions.

It is apparent that the introduction of a fifth substituent onto the cyclopentane ring has markedly altered some of the chemistry of the functional groups attached to the ring. These effects can probably be accounted for by the large size of the trimethylsilyl group, since this group will want to adopt the least hindered position on the cyclopentane ring. The conformational analysis of five-membered rings is less straightforward than the analysis of six-membered rings, but it is known that the lowest energy conformation of a monosubstituted cyclopentane has the substituent in the pseudo equatorial position attached to the carbon atom at the flap position of an envelope conformation.[6] It is thus likely that in compounds **18**−**21**, the trimethylsilyl group occupies this position. The effect of this will be to lock the other four substituents into pseudo axial positions as shown in Figure 2. In contrast, the non-silylated compounds **2a**,**b** are likely to be conformationally flexible as each of the substituents will occupy the least hindered conformation for some of the time. Hence, there is a lower entropic cost associated with cyclization reactions involving the silylated compounds than the corresponding non-silylated compounds. This explains why ozonolysis of acid **1** gives bicyclic hemiacetals **2a**,**b**, while ozonolysis of acid **17a** gives tricyclic hemiacetals **18a**,**b**, and why the further cyclization of **18a**,**b** to **20** is so facile.

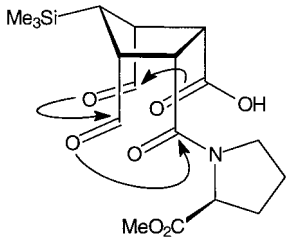

Figure 2. The likely minimum energy conformation of trimethylsilyl substituted cyclopentanes showing the axial location of the carbonyl substituents. Arrows indicate cyclizations which are facile due to the conformation of the molecules.

Conclusions

The desymmetrization of readily available, achiral *endo*-norborn-5-ene-2,3-dicarboxylic anhydride derivatives by methyl (*S*)-prolinate followed by ozonolysis of the resulting acid provides a versatile and concise approach to the synthesis of enantiomerically pure tetra- and penta-substituted cyclopentanes in which the cyclopentane substituents are syn to one another. The initial products of this chemistry are hemiacetals and are highly functionalized to allow further manipulation. It is possible to carry out regioselective reactions on the hemiacetals, and they react diastereoselectively with allylindium to give further derivatized products. The proline auxiliary can be removed from the cyclopentane derivatives under mild conditions by acid catalyzed γ-lactone formation.

Experimental Section

^{1}H NMR spectra were recorded at 250 MHz and at 293K in $CDCl_3$. ^{13}C NMR spectra were recorded at 62.5 MHz and at 293K in $CDCl_3$. Infrared spectra were recorded on a FTIR spectrometer, and only characteristic absorptions are reported. Mass spectra were recorded using the FAB technique (Cs^+ ion bombardment at 25kV) or by chemical ionization (CI) with ammonia. Only significant fragment ions are reported, and only molecular ions are assigned. Optical rotations are reported along with the solvent and concentration in grams/100 mL. Melting points are uncorrected. Elemental analyses were performed within the chemistry department.

All X-ray crystallographic measurements were made at 150 K by following previously described procedures.[18] Crystal data for compound **5**: $C_{15}H_{21}NO_6$ (FW 311.33); orthorhombic; space group $P2_12_12_1$; a = 7.891(2), b = 18.499(4), and c = 31.080(6) Å; V = 4537(2) Å^3; Z = 12; D_c = 1.367 Mg m^{-3}; $F(000)$ = 1992. For compound **6**: $C_{22}H_{24}NO_7Br$ (FW 494.33); orthorhombic; space group $P2_12_12_1$; a = 6.376(2), b = 10.413(2), and c = 32.604(7) Å; V = 2164.7(9) Å^3; Z = 4; D_c = 1.517 Mg m^{-3}; $F(000)$ = 1016. For compound **14**: $C_{12}H_{14}O_4$ (FW 222.23); orthorhombic; space group $P2_12_12_1$; a = 5.712(1), b = 12.258(1), and c = 15.413(2) Å; V = 1079.2(3) Å^3; Z = 4; D_c = 1.368 Mg m^{-3}; $F(000)$ = 472. The structures were solved by direct methods

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(SHELXS86)[19] and refined on F^2 by full-matrix least-squares (SHELXL93)[20] using all unique data corrected for Lorentz and polarization factors. An absorption correction (DIFABS)[21] was applied for the data of compound **6**. The structures were finally refined (6666 data and 601 parameters for **5**; 3087 data and 281 parameters for **6**; 1679 data and 145 parameters for **14**) to R [on F, $F_o > 4\sigma(F_o)$] and wR [on F^2, all data] values of 0.0421 and 0.0982 respectively, for **5**, 0.0445 and 0.1072, respectively, for **6**, and 0.0366 and 0.0751, respectively, for **14**. The Flack parameter in SHELXL93 refined to a final value of 0.01(2) for **6**, confirming that the absolute structure for this compound had been determined correctly. However, the absolute structures for **5** and **14** were uncertain due to the absence of significant anomalous scatter in these molecules. Further details of data collection and structure refinement, atom coordinates, thermal coefficients, hydrogen atom parameters, and bond lengths and angles are available from the Cambridge Crystallographic Data Centre.[22]

Hemiacetals 2a,b. A solution of amido acid **1**[2] (1.0 g, 3.4 mmol) in CH_2Cl_2 (40 mL) was cooled to −78 °C and treated with ozone until a permanent blue color was observed. Dimethyl sulfide (1.3 mL, 17.2 mmol) was then added, and the reaction allowed to stir at room temperature for 16 h. The solvents were evaporated in vacuo, and the residue was subjected to flash chromatography using EtOAc as eluent to give (R_f = 0.14) hemiacetals **2a**,**b** (1.0 g, 92%) as a white powder: mp 44−47 °C. $[\alpha]^{22}_D$ −64.4 (c = 1, $CHCl_3$). IR: 3406, 3019, 2950, 1732, 163. ^{1}H NMR: 1.9−2.4 (m, 5), 2.6−3.3 (m, 3), 3.4−3.55 (m, 2), 3.6−3.9 (m, 2), 3.69 and 3.72 (2 × s, 3), 4.5−4.6 (m, 1), 5.7−5.9 (m, 1), 6.73 (d, 1, J = 13.3), 9.68 and 9.76 (2 × d, 1, J = 1.8 and 2.2). ^{13}C NMR: 24.6, 24.8, 25.9, 30.8, 29.1, 29.2, 43.8, 44.2, 46.2, 47.7, 47.8, 47.9, 48.1, 49.4, 52.2, 52.3, 56.5, 58.4, 59.0, 59.1, 100.3, 103.4, 170.1, 171.2, 171.7, 172.5, 175.5, 176.5, 201.2, 201.3. CI-MS *m*/*e* (rel intensity): 326 (M^+ + 1, 8), 128 (100). HRMS (CI) *m*/*e*: 366.1240 (MH^+ $C_{15}H_{20}NO_7$ requires 366.1239). Anal. Calcd for $C_{15}H_{19}NO_7 \cdot 0.5H_2O$: C, 53.9; H, 6.0; N, 4.2. Found: C, 54.0; H, 5.9; N, 3.8.

[3.2.1]Bicyclic Lactone 4. Hemiacetals **2a**,**b** (1.0 g, 3.1 mmol) were dissolved in MeOH (15 mL) and cooled (0 °C), and sodium borohydride (0.6 g, 15.9 mmol) was cautiously added. The resulting solution was stirred at room temperature for 5 h, the solvent was then evaporated in vacuo, and the residue was subjected to flash chromatography using 90% EtOAc/10% MeOH as eluent to give (R_f = 0.22; 50% EtOAc, 50% MeOH) lactone **4** (0.8 g, 85%) as a white powder: mp 47−50 °C. IR: 3430, 3020, 1748, 1634. ^{1}H NMR: 1.8−2.3 (m, 6), 2.4−2.6 (m, 1), 2.65−2.8 (m, 1), 3.2−3.3 (m, 1), 3.41 (t, 1, J = 7.4), 3.5−3.9 (m, 5), 3.72 (s, 3), 4.05 (dd, 1, J = 10.9, 3.7), 4.3−5.0 (brs, 1), 4.63 (dd, 1, J = 8.1, 2.9). FAB-MS *m*/*e* (rel intensity): 334 (M^+ + 23, 40), 312 (M^+ + 1, 100). HRMS (FAB) *m*/*e*: 312.1430 (MH^+ $C_{15}H_{22}NO_6$ requires 312.1447).

[3.3.0]Bicyclic Lactone 5. Lactone **4** (0.5 g, 1.6 mmol) was dissolved in $CHCl_3$ (20 mL) and allowed to stand at room temperature for 2 days. The solvent was then evaporated in vacuo to give lactone **5** (0.5 g, 100%) as a crystalline solid: mp 91−93 °C. $[\alpha]^{22}_D$ −48.4 (c = 1, $CHCl_3$). IR: 3448, 3017, 2961, 1747, 1634. ^{1}H NMR: 1.3−2.3 (m, 6), 2.6−2.85 (m, 1), 3.0−3.2 (m, 1), 3.3−3.4 (m, 2), 3.6−3.8 (m, 3), 3.77 (s, 3), 3.9−4.0 (m, 1), 4.31 (dd, 1, J = 8.9, 5.0), 4.52 (t, 1, J = 8.9), 4.67 (dd, 1, J = 8.8, 3.4). ^{13}C NMR: 24.7, 29.2, 35.2, 39.1, 46.0, 47.8, 48.6, 50.7, 52.6, 58.1, 62.1, 74.4, 171.7, 173.3, 178.4. CI-MS *m*/*e* (rel intensity): 312 (M^+ + 1, 76), 200 (100). HRMS (CI) *m*/*e*: 312.1447 (MH^+ $C_{15}H_{22}NO_6$ requires 312.1447).

***p*-Bromobenzoate 6.** Triethylamine (0.2 mL, 1.3 mmol) was added to a cooled (0 °C) suspension of lactone **4** (0.20 g, 0.64 mmol) and *p*-bromobenzoyl chloride (0.14 g, 0.64 mmol) in CH_2Cl_2 (3 mL). The reaction mixture was stirred at room temperature for 18 h and subsequently washed with 0.5M HCl, saturated aqueous Na_2CO_3, and H_2O and dried ($MgSO_4$). The solvent was evaporated in vacuo, and the residue was subjected to flash chromatography using EtOAc as eluent to give (R_f = 0.28) *p*-bromobenzoate **6** (0.04 g, 13%) as a clear crystalline solid: mp 170−173 °C. $[\alpha]^{23}_D$ +36.8 (c = 1, $CHCl_3$). IR: 3019, 2954, 1745, 1719, 1634. ^{1}H NMR: 1.67 (dd, 1, J = 6.6, 3.7), 1.9−2.3 (m, 4), 2.4−2.55 (m, 1), 2.6−2.7 (m, 2), 3.1−3.15 (m, 2), 3.58−3.63 (m, 2), 3.69 (s, 3), 4.1−4.6 (m, 5), 7.54 (AA′BB′-d, 2, J = 8.5), 7.89 (AA′BB′-d, 2, J = 8.5). ^{13}C NMR: 24.9, 28.8, 31.3, 34.9, 39.2, 46.8, 47.7, 49.1, 52.4, 58.6, 64.8, 73.0, 128.1, 128.9, 131.3, 131.7, 165.6, 168.8, 170.1, 172.4. CI-MS *m*/*e* (rel intensity): 513, 511 (M^+ + 18, 31), 496, 494 (M^+ + 1, 100), 416 (85). HRMS (CI) *m*/*e*: 494.0814 (MH^+ $C_{22}H_{25}NO_7{}^{79}Br$ requires 494.0814). Anal. Calcd for $C_{22}H_{24}NO_7Br$: C, 53.4; H, 4.9; N, 2.8. Found: C, 53.1; H, 5.1; N, 3.1.

***p*-Bromobenzoate 7.** Triethylamine (0.11 mL, 0.78 mmol) was added to a cooled (0 °C) suspension of lactone **5** (0.12 g, 0.32 mmol) and *p*-bromobenzoyl chloride (0.11 g, 0.42 mmol) in CH_2Cl_2 (3 mL). The reaction mixture was stirred at room temperature for 18 h and subsequently washed with 0.5M HCl, saturated aqueous Na_2CO_3, and H_2O, and dried ($MgSO_4$). The solvent was evaporated in vacuo, and the residue was subjected to dry flash silica chromatography, eluting with CH_2Cl_2 to remove the high running impurities and finally with EtOAc to afford (R_f = 0.35; EtOAc) *p*-bromobenzoate **7** (0.16 g, 84%): mp 57−61 °C. $[\alpha]^{23}_D$ +40.6 (c = 1, $CHCl_3$). IR: 2954, 1748, 1719, 1636. ^{1}H NMR: 1.8−2.3 (m, 6), 2.7−2.9 (m, 1), 3.0−3.2 (m, 1), 3.39 (dd, 1, J = 11.8, 8.9), 3.63 (dd, 1, J = 8.9, 7.1), 3.6−3.7 (m, 2), 3.71 (s, 3), 4.2−4.7 (m, 5), 7.61 (AA′BB′-d, 2, J = 8.5), 7.91 (AA′BB′-d, 2, J = 8.5). ^{13}C NMR: 24.8, 29.2, 35.4, 38.7, 45.8, 47.0, 47.8, 48.9, 52.2, 58.6, 64.9, 74.3, 128.1, 129.1, 131.0, 131.8, 165.5, 170.7, 172.4, 177.9. CI-MS *m*/*e* (rel intensity): 496, 494 (M^+ + 1, 100), 416 (75). HRMS (CI) *m*/*e*: 494.0814 (MH^+ $C_{22}H_{25}NO_7Br$ requires 494.0814). Anal. Calcd for $C_{22}H_{24}NO_7{}^{79}Br \cdot EtOAc$: C, 53.8; H, 5.5; N, 2.4. Found: C, 53.8; H, 5.4; N,2.5.

Aldehyde 8. A solution of oxalyl chloride (0.1 mL, 1.3 mmol) in dry CH_2Cl_2 (10 mL) was cooled (−78 °C) and treated with dimethyl sulfoxide (0.15 mL, 1.9 mmol) to give an effervescent mixture. The resulting solution was stirred for 10 min at −78 °C before being treated with lactone **5** (0.20 g, 0.64 mmol) dissolved in CH_2Cl_2 (1 mL) to give a white precipitate. After warming to −66 °C for 10 min, the mixture was again cooled (−78 °C) and treated with Et_3N (0.5 mL, 3.8 mmol), before being stirred at room temperature for 2 h. The solvent was evaporated in vacuo, and the residue was subjected to flash chromatography using EtOAc as eluent to give (R_f = 0.07) aldehyde **8** (0.13 g, 65%) as a white crystalline solid: mp 84−87 °C. $[\alpha]^{22}_D$ −37.7 (c = 1, $CHCl_3$). IR: 3017, 2978, 2955, 1748, 1721, 1634. ^{1}H NMR: 1.9−2.6 (m, 6), 2.9−3.05 (m, 1), 3.1−3.3 (m, 1), 3.43 (dd, 1, J = 11.2, 9.3), 3.65−3.8 (m, 3), 3.73 (s, 3), 4.34 (dd, 1, J = 9.1, 4.8), 4.5−4.6 (m, 1), 4.52 (t, 1, J = 8.9), 9.76 (d, 1, J = 2.1). ^{13}C NMR: 24.8, 29.2, 33.4, 39.3, 46.3, 47.8, 48.1, 52.2, 57.4, 58.9, 73.1, 169.7, 172.3, 176.8, 201.2. CI-MS *m*/*e* (rel intensity): 310 (M^+ + 1, 100), 282 (16), 250 (13). HRMS (CI) *m*/*e*: 310.1291 (MH^+ $C_{15}H_{20}NO_6$ requires 310.1291). Anal. Calcd for $C_{15}H_{19}NO_6$: C, 58.3; H, 6.2; N, 4.5. Found: C, 58.3; H, 6.4; N, 4.3.

[3.3.0]Bicyclic Lactone 5 from Aldehyde 8. Aldehyde **8** (0.05 g, 0.16 mmol) was dissolved in methanol (5 mL) and cooled to 0 °C, after which, sodium borohydride (0.012 g, 0.32 mmol) was added. After 14 h of stirring, the solvent was evaporated in vacuo, and the residue was subjected to dry flash chromatography[23] using EtOAc as eluent to give (R_f = 0.07), lactone **5** (0.04 g, 80%) as a white powder. Spectroscopic data for compound **5** were reported above.

Dialdehyde 9. A solution of oxalyl chloride (0.06 mL, 0.64 mmol) in dry CH_2Cl_2 (8 mL) was cooled (−78 °C) and treated with dimethyl sulfoxide (0.1 mL, 1.9 mmol) to give an effer-

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(22) The authors have deposited the atomic coordinates for **5**, **6**, and **14** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.
(23) Harwood, L. M. *Aldrichimica Acta* **1985**, *18*, 25.

vescent mixture. The resulting solution was stirred for 10 min at −78 °C before being treated with lactone **4** (0.20 g, 0.64 mmol), dissolved in CH_2Cl_2 (1 mL) to give a white precipitate. After 10 min of warming to −66 °C, the mixture was again cooled (−78 °C) and treated with Et_3N (0.5 mL, 3.8 mmol), before being stirred at room temperature for 2 h. The solvent was evaporated in vacuo, and the residue was subjected to flash chromatography using EtOAc as eluent to give (R_f = 0.24) dialdehyde **9** (0.121 g, 49%) as a clear oil. $[\alpha]^{23}_D$ −31.8 (c = 0.5, $CHCl_3$). IR: 2953, 1736, 1632. ^{1}H NMR: 2.05−2.2 (m, 5), 2.25 (s, 3), 2.7−2.9 (m, 1), 2.9−3.05 (m, 1), 3.1−3.2 (m, 1), 3.47 (dd, 1, J = 10.0, 6.8), 3.6−3.7 (m, 3), 3.74 (s, 3), 4.57 (dd, 1, J = 8.5, 3.7), 5.06 (d, 1, J = 11.8), 5.34 (d, 1, J = 11.8 Hz), 9.73 (d, 1, J = 3.2), 9.89 (d, 1, J = 1.9). ^{13}C NMR: 15.6, 24.8, 26.7, 29.2, 45.8, 47.7, 50.0, 50.4, 52.3, 53.6, 58.7, 69.3, 169.8, 170.1, 172.0, 200.7, 201.8. CI-MS *m/e* (rel intensity): 386 (M^+ + 1, 100), 368 (7), 324 (10). HRMS (CI) *m/e*: 386.1273 (MH^+ $C_{17}H_{24}NO_7S$ requires 386.1273).

Acetal 12. To a well-stirred solution of hemiacetals **2a**,**b** (1.0 g, 3.1 mmol) in 0.5 M HCl (10 mL), containing 10% ethanol was added allyl bromide (0.3 mL, 3.4 mmol) and indium powder (0.55 g, 4.0 mmol). The reaction was allowed to proceed until no hemiacetal **2a**,**b** remained (ca. 14 h), after which the solvent was evaporated in vacuo. The resulting residue was subjected to flash chromatography using 80% EtOAc/20% Petrol as eluent to give (R_f = 0.12; EtOAc) acetal **12** (0.35 g, 33%) as a white powder: mp 129−131 °C. $[\alpha]^{23}_D$ −36.6 (c = 1, $CHCl_3$). IR: 3073, 3018, 2928, 1742, 1613. ^{1}H NMR: 1.9−2.5 (m, 8), 3.35−4.05 (m, 6), 3.77 (s, 3), 4.59 (dd, 1, J = 5.5, 3.0), 5.1−5.3 (m, 2), 5.75−6.0 (m, 2), 7.23 (d, 1, J = 13.5). ^{13}C NMR: 24.5, 28.0, 29.1, 40.6, 44.3, 45.8, 47.9, 49.0, 52.7, 54.8, 58.4, 71.0, 100.9, 117.7, 134.4, 173.2, 173.6, 176.2. CI-MS *m/e* (rel intensity): 350 (M^+ + 1, 15), 259 (12). HRMS (CI) *m/e*: 350.1604 (MH^+ $C_{18}H_{24}NO_6$ requires 350.1604).

Alcohols 13a,b. To a well-stirred solution of hemiacetals **2a**,**b** (0.25 g, 0.77 mmol) in 0.5 M HCl (5 mL), containing 10% ethanol was added allyl bromide (0.15 mL, 1.9 mmol) and indium powder (0.2 g, 1.6 mmol). The reaction was allowed to proceed until no hemiacetal **2a**,**b** remained (ca. 14 h), after which the solvent was evaporated in vacuo. The resulting residue was subjected to flash chromatography using 80% EtOAc/20% Petrol as eluent to give (R_f = 0.46; EtOAc) minor diastereomer **13b** (0.04 g, 13%) and (R_f = 0.41; EtOAc) major diastereomer **13a** (0.15 g, 50%) as clear oils. Data for **13b**. $[\alpha]^{23}_D$ +6.4 (c = 1, $CHCl_3$). IR: 3466, 3074, 2925, 1750, 1640. ^{1}H NMR: 1.9−2.6 (m, 11), 2.7−2.85 (m, 1), 3.3−3.4 (m, 2), 3.65 (m, 3), 3.72 (s, 3), 4.53 (dd, 1, J = 9.0, 5.0), 4.61 (q, 1, J = 6.5), 5.1−5.3 (m, 4), 5.7−6.0 (m, 2). ^{13}C NMR: 25.0, 29.2, 32.6, 40.0, 41.4, 44.2, 46.3, 48.2, 50.2, 52.5, 52.9, 58.7, 69.4, 86.2, 117.8, 118.9, 132.1, 135.1, 172.9, 173.6, 177.9. CI-MS *m/e* (rel intensity): 392 (M^+ + 1, 100), 350 (5). HRMS (CI) *m/e*: 392.2073 (MH^+ $C_{21}H_{30}NO_6$ requires 392.2073). Data for **13a**. $[\alpha]^{23}_D$ −4.2 (c = 1, $CHCl_3$). IR: 3486, 3075, 2952, 1747, 1633. ^{1}H NMR: 1.9−2.25 (m, 11), 3.2−3.4 (m, 1), 3.36 (dd, 1, J = 11.5, 9.5), 3.6−4.0 (m, 3), 3.64 (dd, 1, J = 9.5, 7.5), 4.55−4.7 (m, 2), 5.1−5.3 (m, 4), 5.7−6.0 (m, 2). ^{13}C NMR: 24.6, 29.3, 35.2, 40.1, 40.7, 45.0, 46.4, 47.8, 49.5, 52.6, 54.3, 58.2, 70.8, 86.3, 117.4, 119.0, 132.1, 134.7, 172.3, 174.2, 177.8. CI-MS *m/e* (rel intensity): 392 (M^+ + 1, 100), 350 (6). HRMS (CI) *m/e*: 392.2073 (MH^+ $C_{21}H_{30}NO_6$ requires 392.2073).

Bis-lactone 14. A solution of acetal **12** (0.05 g, 0.14 mmol) and sodium borohydride (0.027 g, 0.72 mmol) in MeOH (2 mL) was stirred at room temperature for 5 h. The solvent was subsequently evaporated in vacuo, and the residue was subjected to dry flash silica chromatography,[23] eluting with 50% EtOAc/50% MeOH. Following evaporation of the solvent, the resulting diol was redissolved in CH_2Cl_2 (2 mL), and *p*-toluenesulfonic acid monohydrate (0.25 g, 1.4 mmol) was added. After 18 h of stirring, the mixture was washed with saturated aqueous Na_2CO_3 and dried ($MgSO_4$), and the solvent was evaporated in vacuo. Purification by flash chromatography using 80% EtOAc/20% Petrol as eluent yielded (R_f = 0.20) bis-lactone **14** (0.03 g, 94%) as a white solid: mp 62−65 °C. $[\alpha]^{23}_D$ −3.9 (c = 1, $CHCl_3$). IR: 2924, 1773. ^{1}H NMR: 1.62 (dt, 1, J = 14.5, 5.5), 2.3−2.7 (m, 3), 2.8−3.0 (m, 1), 3.3−3.4 (m, 1), 3.4−3.5 (m, 2), 4.09 (dd, 1, J = 9.5, 3.5), 4.20 (q, 1, J = 6.0), 4.44 (dd, 1, J = 9.5, 6.5), 5.1−5.2 (m, 2), 5.65−5.9 (m, 1). ^{13}C NMR: 36.1, 39.3, 43.2, 47.3, 47.6, 48.8, 72.1, 84.7, 119.5, 131.5, 174.6, 175.7. CI-MS *m/e* (rel intensity): 240 (M^+ + 18, 100), 223 (M^+ + 1, 9). HRMS (CI) *m/e*: 240.1236 (M + NH_4^+ $C_{12}H_{18}NO_4$ requires 240.1236).

Bis-lactone 15. A solution of alcohol **13a** (0.08 g, 0.20 mmol) and *p*-toluenesulfonic acid monohydrate (0.4 g, 2.0 mmol) in CH_2Cl_2 (2 mL) was stirred at room temperature for 18 h. The reaction mixture was subsequently washed with saturated aqueous Na_2CO_3 solution and dried ($MgSO_4$), and the solvent was evaporated *in vacuo*. Purification by flash chromatography using 70% Petrol/30% EtOAc yielded (R_f = 0.14) meso bis-lactone **15** (0.03 g, 56%) as a clear oil. $[\alpha]^{23}_D$ 0.0 (c = 1, $CHCl_3$). IR: 3078, 2932, 1772, 1642. ^{1}H NMR: 1.62 (dt, 1, J 14.5, 5.0), 2.3−2.6 (m, 5), 2.8−3.0 (m, 2), 3.3−3.4 (m, 2), 4.24 (q, 2, J 5.0), 5.0−5.2 (m, 4), 5.1−5.4 (m, 2). ^{13}C NMR: 36.2, 39.4, 47.5, 48.1, 84.2, 119.6, 131.6, 174.6. CI-MS *m/e* (rel intensity): 280 (M^+ + 18, 100), 263 (M^+ + 1, 15). HRMS (CI) *m/e*: 280.1549 (M + NH_4^+ $C_{12}H_{18}NO_4$ requires 280.1549).

Amido Acids 17a,b. Triethylamine (2.7 mL, 19.1 mmol) was added to a cooled (0 °C) suspension of anhydride **16**[15] (1.5 g, 6.4 mmol) and methyl (*S*)-prolinate hydrochloride (2.1 g, 12.7 mmol) in CH_2Cl_2 (16 mL). The resulting mixture was stirred at room temperature for 24 h and subsequently washed with 0.5 M HCl and H_2O and dried ($MgSO_4$). The solvent was evaporated in vacuo to leave amido acids **17a**,**b** (2.2 g, 94%) as a 3:1 ratio of diastereomers as a yellow oil. IR: 3500−2300, 3008, 2953, 1735, 1654. ^{1}H NMR (only peaks corresponding to the major diastereomer **17a** are reported): 0.09 (s, 9), 1.04 (s, 1), 2.0−2.3 (m, 4), 3.3−3.5 (m, 4), 3.6−3.9 (m, 2), 3.77 (s, 3), 4.50 (dd, 1, J = 8.7, 3.9), 6.2−6.3 (m, 2), 9.25 (brs, 1). ^{13}C NMR (only peaks corresponding to the major diastereomer **17a** are reported): −0.3, 24.8, 29.0, 47.0, 49.7, 49.9, 50.5, 51.2, 51.7, 52.1, 58.9, 133.7, 135.1, 172.1, 172.7, 176.2. CI-MS *m/e* (rel intensity): 366 (M^+ + 1, 5), 294 (11), 130 (100). HRMS (CI) *m/e*: 366.1737 (MH^+ $C_{18}H_{28}NO_5Si$ requires 366.1737).

Hemiacetals 18a,b. A solution of amido acids **17a**,**b** (0.5 g, 1.4 mmol) in CH_2Cl_2 (50 mL) was cooled to −78 °C and treated with ozone until a permanent blue color was observed. Dimethyl sulfide (1.1 mL, 13.7 mmol) was then added, and the reaction mixture was allowed to stir at room temperature for 16 h. The solvents were evaporated in vacuo, and the residue was subjected to flash chromatography using EtOAc as eluent to give (R_f = 0.52) hemiacetals **18a**,**b** (0.43 g, 79%) as a yellow powder: mp 79−83 °C. $[\alpha]^{23}_D$ −26.9 (c = 1, $CHCl_3$). IR: 3388, 2953, 1744, 1630. ^{1}H NMR: 0.17 (s, 9), 0.98 and 1.10 (2 × t, 1, J = 3.3 and 3.5), 1.85−2.2 (m, 4), 2.2−3.8 (m, 6), 3.71 and 3.73 (2 × s, 3), 4.5−4.6 (m, 1), 5.43 (dd, 1, J = 9.6, 4.3), 5.78 and 5.89 (2 × d, 1, J = 6.7 and 6.3), 8.55 (d, 1, J = 9.6). ^{13}C NMR: −0.7 and −0.3, 24.82 and 24.84, 28.9 and 29.1, 31.4 and 34.0, 43.8 and 44.0, 44.4 and 44.9, 46.0 and 47.8, 47.2 and 47.9, 52.4 and 53.0, 55.0 and 55.6, 59.0 and 59.7, 92.8 and 96.9, 99.5 and 102.8, 168.2 and 171.0, 172.2 and 172.7, 176.0 and 177.0. CI-MS *m/e* (rel intensity): 398 (M^+ + 1, 10), 286 (8), 130 (100). HRMS (CI) *m/e*: 398.1635 (MH^+ $C_{18}H_{28}NO_7Si$ requires 398.1635).

Bis-lactone 19. A solution of oxalyl chloride (0.09 mL, 1.0 mmol) in dry CH_2Cl_2 (3 mL) was cooled (−78 °C) and treated with dimethyl sulfoxide (0.1 mL, 1.5 mmol) to give an effervescent mixture. The resulting solution was stirred for 10 min at −78 °C before being treated with hemiacetals **18a**,**b** (0.2 g, 0.50 mmol) dissolved in CH_2Cl_2 (1 mL) to give a white precipitate. After 10 min of warming to −60 °C, the mixture was again cooled (−78 °C) and treated with Et_3N (0.4 mL, 3.0 mmol), before being stirred at room temperature for 2 h. The solvent was evaporated in vacuo, and the residue was subjected to flash chromatography using EtOAc as eluent to give (R_f = 0.31) bis-lactone **19** (0.11 g, 55%) as a white powder: mp 114−117 °C. $[\alpha]^{22}_D$ −43.0 (c = 1, $CHCl_3$). IR: 3019, 2956, 1798, 1765, 1648. ^{1}H NMR: 0.13 (s, 9), 1.4−1.5 (m, 1), 1.7−2.2 (m, 4), 3.0−3.7 (m, 6), 3.66 (s, 3), 4.4−4.5 (m, 1), 5.99 (d, 1, J = 4.9). ^{13}C NMR: −1.5, 24.7, 29.7, 32.9, 43.8, 45.2, 47.3, 47.9, 50.2, 52.2, 59.0, 100.2, 167.5, 169.4, 172.2, 175.5. CI-MS *m/e* (rel intensity): 413 (M^+ + 18, 16), 396 (M^+ + 1, 9). HRMS

(CI) *m/e*: 396.1479 (MH^+ $C_{18}H_{26}NO_7Si$ requires 396.1479). Anal. Calcd for $C_{18}H_{25}NO_7Si$: C, 54.7; H, 6.4; N, 3.5. Found: C, 54.9; H, 6.4; N, 3.8.

Bis-lactone 20. A solution of hemiacetals **18a**,**b** (0.10 g, 0.25 mmol) and *p*-toluenesulfonic acid (0.10 g, 0.50 mmol) in CH_2Cl_2 (1 mL) was stirred at room temperature for 24 h. The reaction mixture was subsequently washed with saturated aqueous Na_2CO_3 and H_2O and dried ($MgSO_4$), and the solvent was evaporated in vacuo. Purification by flash chromatography using 50% Petrol/50% EtOAc as eluent yielded ($R_f = 0.42$) bis-lactone **20** (0.024 g, 36%) as a white powder: mp 216−218 °C. IR: 3020, 2976, 1776. ^{1}H NMR: 0.21 (s, 9), 1.4−1.5 (m, 1), 3.3−3.4 (m, 4), 5.84 (d, 1, $J = 5.4$). ^{13}C NMR: −0.5, 29.3, 45.5, 46.4, 100.3, 172.8. CI-MS *m/e* (rel intensity): 286 ($M^+ + 18$, 100). HRMS (CI) *m/e*: 286.1111 ($M + NH_4^+$ $C_{12}H_{20}NO_5Si$ requires 286.1111).

Lactone 21. Hemiacetals **18a**,**b** (0.25 g, 1.1 mmol) were dissolved in MeOH (8 mL) and cooled (0 °C), and sodium borohydride (0.2 g, 5.0 mmol) was cautiously added. The resulting solution was stirred at room temperature for 16 h, the solvent was then evaporated in vacuo, and the residue was redissolved in CH_2Cl_2. The solution was subsequently washed with 1 M HCl and dried ($MgSO_4$), and the solvent was evaporated in vacuo. Purification by flash chromatography using 2% MeOH/98% ether as eluent afforded ($R_f = 0.40$; 10% MeOH/90% ether) lactone **21** (0.27 g, 61%) as a white powder: mp 55−59 °C. $[\alpha]^{22}_D$ −56.9 ($c = 1$, $CHCl_3$). IR: 3450, 3018, 2954, 1757, 1634. ^{1}H NMR: 0.12 (s, 9), 1.57 (dd, 1, $J = 9.3, 6.3$), 2.0−2.3 (m, 4), 2.94 (ddd, 1, $J = 12.0, 9.1, 3.0$), 3.1−3.3 (m, 2), 3.55−4.0 (m, 5), 3.73 (s, 3), 4.21 (t, 1, $J = 8.9$), 4.34 (t, 1, $J = 8.9$), 4.53 (dd, 1, $J = 8.8, 3.1$), 4.65 (brs, 1). ^{13}C NMR: −0.2, 24.7, 29.2, 36.6, 45.4, 47.5, 49.2, 49.7, 49.9, 52.6, 58.9, 62.7, 71.5, 170.5, 173.7, 178.4. CI-MS *m/e* (rel intensity): 384 ($M^+ + 1$, 79), 272 (43), 130 (100). HRMS (CI) *m/e*: 384.1842 (MH^+ $C_{18}H_{30}NO_6Si$ requires 384.1842).

Bis-lactone 22. A solution of lactone **21** (0.05 g, 0.13 mmol) and *p*-toluenesulfonic acid (0.024 g, 0.13 mmol) in CH_2Cl_2 (0.5 mL) was stirred at room temperature for 18 h. The reaction mixture was subsequently washed with 0.5M HCl, saturated aqueous Na_2CO_3, and H_2O and dried ($MgSO_4$), and the solvent was evaporated in vacuo. Purification by flash chromatography using ether as eluent yielded ($R_f = 0.23$) bis-lactone **22** (0.025 g, 75%) as a crystalline solid: mp 155−157 °C. IR: 3023, 2951, 1782. ^{1}H NMR: 0.15 (s, 9), 1.83 (t, 1, $J = 8.1$), 3.2−3.4 (m, 4), 4.11 (dd, 1, $J = 9.7, 6.5$), 4.43 (dd, 1, $J = 9.7, 8.8$). ^{13}C NMR: −2.2, 35.4, 45.6, 48.8, 70.6, 175.4. CI-MS *m/e* (rel intensity): 272 ($M^+ + 18$, 100). HRMS (CI) *m/e*: 272.1318 ($M + NH_4^+$ $C_{12}H_{22}NO_4Si$ requires 272.1318). Anal. Calcd for $C_{12}H_{18}O_4Si$: C, 56.7; H, 7.1. Found: C, 56.6; H, 7.3.

Dialdehyde 23. A suspension of hemiacetals **18a**,**b** (0.05 g, 0.13 mmol) and K_2CO_3 (0.09 g, 0.63 mmol) in CH_2Cl_2 (1 mL) was stirred at room temperature for 2 h. The reaction mixture was subsequently washed with 1 M HCl to yield dialdehyde **23** (0.05 g, 100%) as a clear oil. $[\alpha]^{23}_D$ −49.6 ($c = 1$, $CHCl_3$). IR: 3500−2500, 3021, 2955, 1723, 1644. ^{1}H NMR: 0.81 (s, 9), 1.64 (dd, 1, $J = 11.4, 9.2$), 1.9−2.3 (m, 4), 3.0−3.2 (m, 2), 3.5−3.9 (m, 4), 3.69 (s, 3), 4.55 (dd, 1, $J = 8.8, 3.7$), 5.65 (brs, 1), 9.63 (s, 1), 9.89 (d, 1, $J = 1.7$). ^{13}C NMR: −2.7, 24.7, 28.2, 28.9, 44.8, 47.2, 50.8, 52.3, 54.5, 56.1, 58.6, 171.6, 172.7, 175.0, 199.1, 202.3. CI-MS *m/e* (rel intensity): 398 ($M^+ + 1$, 12), 370 (4), 90 (100). HRMS (CI) *m/e*: 398.1635 (MH^+ $C_{18}H_{28}NO_7Si$ requires 398.1635).

Bis-lactone 24. To a well-stirred solution of hemiacetals **18a**,**b** (0.5 g, 1.25 mmol) in 0.5 M HCl (5 mL) and THF (5 mL) were added allyl bromide (0.15 mL, 1.8 mmol) and indium powder (0.15 g, 1.4 mmol). After 20 h of stirring at room temperature, the mixture was extracted with CH_2Cl_2. The combined CH_2Cl_2 layers were washed with H_2O, dried ($MgSO_4$), and evaporated to dryness in vacuo. Addition of hot EtOAc and filtration of the impurities, followed by evaporation of the filtrate in vacuo yielded meso bis-lactone **24** (0.18 g, 43%) as a clear crystalline solid: mp 80−81 °C. $[\alpha]^{23}_D$ ($c = 1$, $CHCl_3$). IR: 3019, 2958, 1780. ^{1}H NMR: 0.22 (s, 9), 1.74 (s, 1), 2.35−2.5 (m, 2), 2.55−2.7 (m, 2), 3.0−3.15 (m, 2), 3.40 (dd, 2, $J = 6.0, 3.0$), 4.40 (td, 2, $J = 6.5, 3.5$), 5.15−5.25 (m, 4), 5.8−6.0 (m, 2). ^{13}C NMR: 0.0, 36.5, 40.0, 50.1, 50.2, 81.7, 119.5, 131.7, 174.4. CI-MS *m/e* (rel intensity): 352 ($M^+ + 18$, 28), 335 ($M^+ + 1$, 11), 286 (100). HRMS (CI) *m/e*: 335.1693 (MH^+ $C_{18}H_{27}O_4Si$ requires 335.1679).

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Supporting Information Available: Copies of the NMR spectra for compounds **4**, **5**, **9**, **12**, **13a**, **13b**, **14**, **15**, **17a**,**b**, **18a**,**b**, **20**, **21**, **23**, and **24** as well as ORTEP diagrams and tables of atomic coordinates, bond lengths, bond angles, and anisotropic displacement factors for compounds **5**, **6**, and **14**. This material is available free of charge via the Internet at http://pubs.acs.org.

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