Bidirectional Asymmetric Allylboration. A Convenient Asymmetric Synthesis of C_2-Symmetric 3-Methylenepentane-1,5-diols and Rapid Access to C_2-Symmetric Spiroketals

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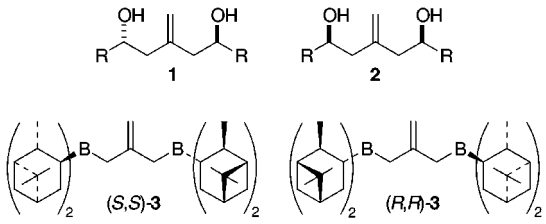
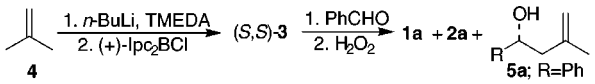
The double allylboration of aldehydes using 1,3-bis(diisopinocampheylboryl)-2-methylenepropanes (*R*,*R*)-**3** and (*S*,*S*)-**3** under Brown's salt-free conditions provides C_2-symmetric 3-methylenepentane-1,5-diols **1** in excellent enantiomeric excess. The absolute stereochemistry of the products was confirmed by a single-crystal X-ray study of bis-Mosher ester **6g**. Desymmetrization and further functionalization of diol **1a** were achieved by treatment of the bis-BOC carbonate **13** with IBr in toluene at −80 °C to give cyclic iodocarbonate **14** as a single diastereomer. This methodology is also applicable in natural product synthesis; enantiomerically pure spiroketals 1,7-dioxaspiro[5.5]-undecanes **18** and **25**, the latter representing an expedient synthesis of the AB ring system of the spongistatins **20**, were easily accessed from simple starting materials in excellent yields and selectivities.

C_2-symmetric 3-methylenepentane-1,5-diols **1** are potentially versatile synthetic intermediates,[1] but to date their utility has been hampered by the fact that the available synthetic methods afford 1:1 mixtures of the desired C_2-symmetric *rac*-**1** and *meso*-**2** isomers.[2] As an extension of the Brown allylboration reaction,[3] we have recently communicated the use of the enantiomeric bis(diisopinocampheylborane)s (*S*,*S*)- and (*R*,*R*)-**3** in bidirectional asymmetric allylboration reactions, providing the first access to highly diastereo- and enantiomerically enriched C_2-symmetric 3-methylenepentane-1,5-diols **1**.[4] Herein we report full experimental details for this method and the application to the synthesis of C_2-symmetric spiroketals.



Scheme 1



Results and Discussion

Double deprotonation of 2-methylpropene **4** with *n*-BuLi−TMEDA, as reported,[2a,5] followed by condensation with 2 equiv of either antipode of commercially available *B*-chlorodiisopinocampheylborane afforded the corresponding bis(diisopinocampheylborane)s (*S*,*S*)- and (*R*,*R*)-**3**. Initial in situ reaction with 2 equiv of benzaldehyde followed by an alkaline H_2O_2 workup afforded an inseparable mixture of 3-methylenepentane-1,5-diols **1a** and **2a** (R = Ph) (60%) accompanied by the product of monoallylboration, 3-methyl-1-phenylbut-3-en-1-ol (**5a**) (30%) (Scheme 1). The diastereomeric ratio (dr) of the mixture of diols **1a** and **2a** (R = Ph) was estimated to be 8:2 (by ^{1}H NMR spectroscopy) in favor of the desired C_2-symmetric isomer **1a**. The reaction was then optimized. First the initially formed 1,3-dilithio-2-methylenepropane was isolated by filtration (35−50%) to remove any monoanion present in solution, as this is known to provide the product of monoallylboration.[6] Second the reaction was conducted under Brown's "salt-free" conditions[7] to improve the selectivity. Gratifyingly, these modifications afforded the desired product **1a** (R = Ph) in good yield (55% from the dianion) and diastereoselectivity and excellent enantioselectivity (see Table 1, entry 1), and reduced the yield of the alcohol byproduct **5a** to <5%.

A range of achiral aldehydes were then allowed to react with both enantiomers of reagent **3** under the optimized conditions to afford the corresponding C_2-symmetric 3-methylenepentane-1,5-diols **1b**−**h** in moderate yields

(1) Alonso, F.; Lorenzo, E.; Yus, M. *Tetrahedron Lett.* **1997**, *38*, 2187.
(2) (a) Bates, R. B.; Beavers, W. A.; Gordon, B. *J. Org. Chem.* **1979**, *44*, 3800. (b) Klein, J.; Medlik-Balan, A.; Meyer, A. Y.; Chorev, M. *Tetrahedron* **1976**, *32*, 1839. (c) Bubnov, Y. N.; Gurskii, M. E.; Pershin, D. G. *Bull. Acad. Sci., USSR, Div. Chem. Sci.* **1987**, *36*, 1107. (d) Imai, T.; Nishida, S. *Synthesis* **1993**, 395. (e) Gómez, C.; Ramón, D. J.; Yus, M. *Tetrahedron* **1993**, *49*, 4117. (f) Kang, S.-K.; Park, D.-C.; Park, C.-H.; Jang, S.-B. *Synth. Commun.* **1995**, *25*, 1359. (g) Majetich, G.; Nishidie, H.; Zhang, Y. *J. Chem. Soc., Perkin Trans. 1* **1995**, 453. (h) Li, C.-J. *Tetrahedron Lett.* **1995**, *36*, 517. (i) Masuyama, Y.; Kagawa, M.; Kurusu, Y. *Chem. Commun.* **1996**, 1585. (j) Krief, A.; Dumont, W. *Tetrahedron Lett.* **1997**, *38*, 657 and references therein.
(3) (a) Brown, H. C.; Jadhav, P. K. *J. Am. Chem. Soc.* **1983**, *105*, 2092. (b) Roush, W. R. Allyl Organometallics. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Heathcock, C. H., Eds.; Pergamon Press: New York, 1991; Vol. 2, pp 1−53 and references therein. (c) Barrett, A. G. M.; Wan, P. W. H. *J. Org. Chem.* **1996**, *61*, 8667 and references therein.
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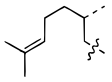
Table 1. Preparation of C_2-Symmetric 3-Methylenepentane-1,5-diols 1

2 RCHO $\xrightarrow{\text{reagent}}$ **1** + **2**

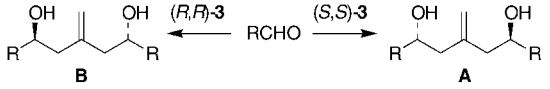
entry	reagent[a]	R	product (%Yield)[b]	dr[c] **1:2**	%ee[c]
1	(*S,S*)-**3**	Ph	**1a** (55)	84:16	>95[d]
2	(*S,S*)-**3**	*i*-Pr	**1b** (41)	93:7	>95[d]
3	(*R,R*)-**3**	*i*-Pr	**1b** (38)	91:9	>95[e]
4	(*S,S*)-**3**	Et	**1c** (45)	93:7	>95[e]
5	(*S,S*)-**3**	*s*-Bu	**1d** (53)	93:7	>95[e]
6	(*S,S*)-**3**	*n*-C_5H_{11}	**1e** (43)	92:8	>95[e]
7	(*S,S*)-**3**	4-$O_2NC_6H_4$	**1f** (51)	95:5	>95[d]
8	(*S,S*)-**3**	4-$MeOC_6H_4$	**1g** (55)	95:5	>95[d]
9	(*S,S*)-**3**	3-$O_2NC_6H_4$	**1h** (47)	94:6	>95[d]
10	(*S,S*)-**3**		**1i** (38)	66:14.5:1[f]	—
11	(*R,R*)-**3**		**1j** (50)	160:22:1[g]	—
12	(*R,R*)-**3**		**1k** (57)	46:6:1[f]	—

[a] Reagent (*S,S*)-**3** derives from (+)-*B*-chlorodiisopinocampheylborane. (*R,R*)-**3** derives from (−)-*B*-chlorodiisopinocampheylborane. [b] All yields are quoted relative to the amount of dianion used. [c] Both the dr and % ee are estimated from the corresponding bis-Mosher esters.[8] [d] (*R,R*) configuration. [e] (*S,S*) configuration. [f] The central 3-methylenepentanediol entity of the major diastereoisomer has the (*R,R*) configuration. [g] The central 3-methylenepentanediol entity of the major diastereoisomer has the (*S,S*) configuration.

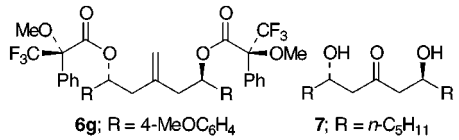
(Table 1, entries 2−9), but with good diastereoselectivities (dr > 91:9) and excellent enantioselectivities (>95% ee). In all examples, the product of monoallylboration **5** was observed but not isolated as it coeluted with the diisopinocampheylborane-derived isopinocampheol. Both 2-nitrobenzaldehyde and pivaldehyde failed to react, presumably on account of SET chemistry or steric congestion. Reaction with homochiral aldehydes (Table 1, entries 10−12) proceeded with substantial reagent control; largely a single isomer was isolated in both the mismatched (entry 10) and matched (entry 11) cases. As expected, when the stereocenter was one atom further removed from the aldehyde, it had no significant influence on the reaction outcome (Table 1, entry 12), the diastereoselectivity being similar to that observed with achiral aldehydes.

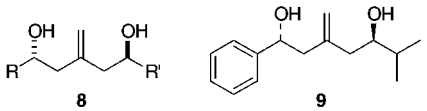
While in principle the diastereoselectivity could be determined directly from the ^{1}H NMR of the (chromatographed) inseparable diol mixture **1** and **2**, it was found that more accurate ratios could be garnered from the ^{1}H NMR of their bis-(*S*)-Mosher (MTPA) esters.[8] This also allowed for determination of the enantiomeric excess of

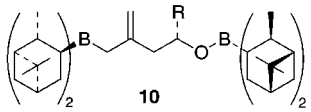
Scheme 2



the diols **1a**−**h**. The absolute stereochemical outcome of the reaction was determined by an X-ray crystallographic analysis of the bis-(*S*)-MTPA ester **6g** (R = 4-MeO−C_6H_4) (see the Supporting Information) derived from the action of (*S,S*)-**3** on *p*-methoxybenzaldehyde, which unequivocally established both the relative and absolute stereochemistries of this compound and, by inference, all the diols in Table 1. Additional confirmation of the absolute stereochemical control of the double allylboration reaction was obtained through ozonolysis of the hexanal derived diol **1e** to dihydroxy ketone **7** (97%). The optical rotation observed {$[\alpha]^{25}_D$ +45.8° (*c* 0.2; $CHCl_3$)} had the sign opposite to that reported for the antipode {$[\alpha]^{25}_D$ −40.4° (*c* 0.2; $CHCl_3$)}.[9] Thus, the reagent (*S,S*)-**3** gives rise to the central 3-methylenepentane-1,5-diol core with the absolute configuration **A** as depicted in Scheme 2, while the (*R,R*)-**3** reagent gives rise to the opposite configuration **B** (note that the absolute configurational descriptors in the adducts, *R,R* vs *S,S*, are dependent on the nature of the R group). These results are in full accord with the established stereoselectivities of other Brown allylborane and aldehyde condensation reactions.[3]







The bis(diisopinocampheylborane) reagents (*S,S*)- and (*R,R*)-**3** would be much more versatile synthons if they could be reacted successively with two different aldehydes, RCHO and R′CHO, to give mixed adducts of type **8**. A number of experiments were conducted utilizing benzaldehyde and isobutyraldehyde as two representative aldehydes: (i) the reagent (*S,S*)-**3** was treated with 1 equiv of benzaldehyde under the normal reaction conditions followed, after 1 h, by 2 equiv of isobutyraldehyde; (ii) the order of addition (and the stoichiometry) was reversed; (iii) the two aldehydes (1.5 equiv) were added as a mixture; (iv) the reaction was conducted with just benzaldehyde, in a limiting quantity (1 equiv). The results from these experiments are as follows. Experiments 1 and 2 yielded both the symmetrical adducts **1a** (15%, 15%) and **1b** (29%, 12%) as the major products along with a small amount of mixed adduct **9** (10%, 4%), respectively. Experiment 3 yielded an approximately statistical distibution of products (41% isolated yield). In the final experiment the bisadduct **1a** was isolated in 27%

(8) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

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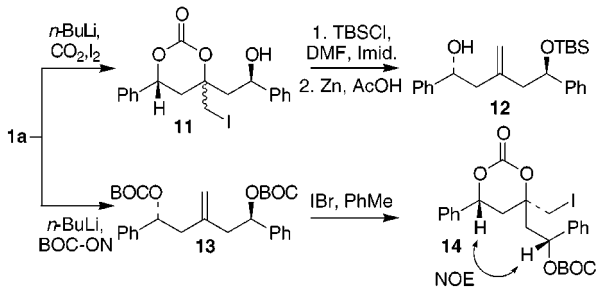
Scheme 3

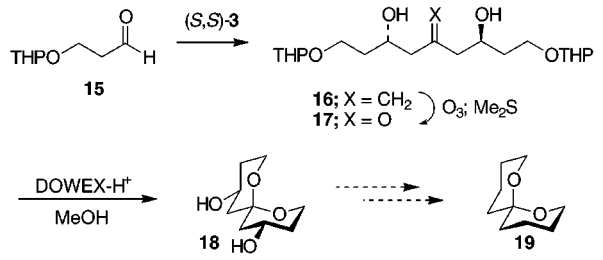


yield with only 1.7% of monoadduct **5a** present. These results clearly show that all things being equal the second allylboration proceeds faster than the first, and the reagents (*R,R*)-**3** and (*S,S*)-**3** appear to be unsuitable for the practical synthesis of nonsymmetrical diols **8** in this manner. A possible explanation for this finding is that bis(diisopinocampheylborane) **3** is stabilized relative to the presumed monoallylboration adduct intermediate **10** by degenerate 1,3-boron migrations. This type of migration has been observed in the analogous achiral 1,3-bis-(dipropylboryl)-2-methylenepropane,[2c] where the three methylene groups were found to be equivalent by ^{1}H NMR spectroscopy.

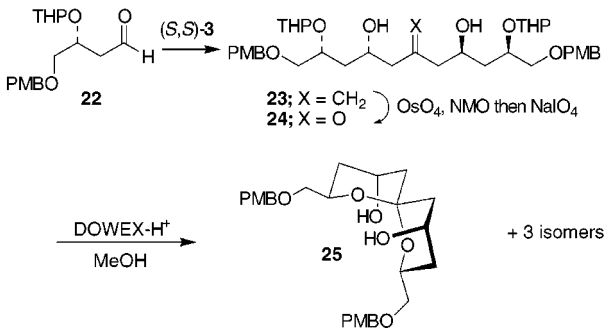
In light of our inability to prepare diols of type **8**, a method for the efficient desymmetrization of diol **1** via intramolecular attack of the central methylene unit by the suitably derivatized alcohol was pursued. Exposing diol **1a** (R = Ph) to iodocarbonate cyclization conditions[10] employing 2.2 equiv of *n*-BuLi, followed by CO_2 and I_2, afforded the desymmetrized cyclic carbonate **11** in a reasonable yield (61%, Scheme 3), but without any selectivity at the quaternary carbon (ca.. 1:1 mixture of diastereoisomers by ^{1}H NMR). The acyclic monoprotected, desymmetrized alcohol **12** was obtained by silylation of **11** followed by treatment with zinc in acetic acid (40%, Scheme 3). While this method had indeed achieved the desired desymmetrization, the lack of selectivity in the iodocyclization step and the poor yield clearly limit its utility. Fortunately, Smith's excellent modification[11] utilizing IBr on the bis-BOC carbonate **13** in toluene at −80 °C afforded iodocarbonate **14** in good isolated yield (82%). In this case the diastereoselectivity was excellent; essentially a single isomer was observed by ^{1}H NMR. The structural assignment was confirmed by NOE measurements, the diagnostic evidence being the presence of an NOE enhancement between the two protons α to the carbonates, firmly placing the phenyl and iodomethylene groups cis on the six-membered ring.

The double allylboration strategy also lends itself to the preparation of enantiomerically pure spiroketals, a widely occurring motif in natural products.[12] 4,10-Dihydroxy-1,7-dioxaspiro[5.5]undecane (**18**) was selected as a target, which has been converted into both enantiomers of 1,7-dioxaspiro[5.5]undecane (**19**), the major components of the sex pheromones of the olive fruit fly.[13]

Scheme 4



Scheme 5



3-(Tetrahydro-2*H*-pyran-2-yl)oxypropanal (**15**)[14] was reacted with (*S,S*)-**3** under the standard reaction conditions to give C_2-symmetric diol **16** (45%, Scheme 4). Due to the presence of the THP protecting groups it proved impossible to determine the diastereomeric excess at this stage. Ozonolysis to dihydroxy ketone **17**, followed by treatment with DOWEX 50WX8-400 resin in methanol, chromatography, and recrystallization afforded the known spiroketal **18**[13] as a single diastereoisomer by ^{13}C and ^{1}H NMR spectroscopy in ca. 33% yield from aldehyde **15**. Although the melting point was slightly lower than that reported, the observed optical rotation and other spectroscopic data were identical to the literature values.[13] Spiroketal **18** was previously synthesized from (*S*)-malic acid in 10 steps and in ca. 10% overall yield; this procedure therefore represents a significant improvement.

As a further demonstration of the power of this methodology, we assayed the synthesis of the AB spiroketal fragment of the spongistatins **20**.[15] These extremely potent inhibitors of cancer cell growth are isolated in miniscule quantities from marine sponges and have been the subject of numerous synthetic efforts,[16] culminating in two total syntheses.[17] A previously published retrosynthetic analysis[18] had shown that a differentially protected hydroxyketone **21** should be a suitable precursor for this product. In addition, an excellent method for the desym-

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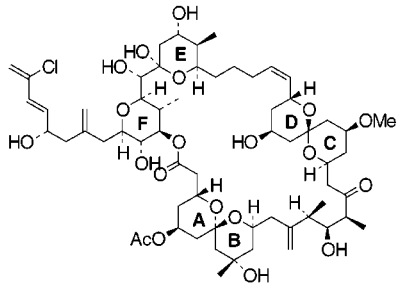
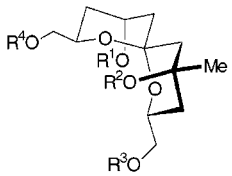
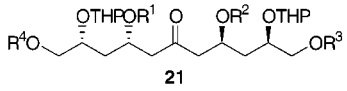


Spongistatin **20**

Excise AB Fragment





21

metrization of a C_2-symmetric analogue of **21** has been published.[19] We sought to prepare a C_2-symmetric version of the spiroketal intermediate **21**. (3*R*)-4-(4-Methoxybenzyloxy)-3-(tetrahydro-2*H*-pyran-2-yl)oxybutanal (**22**) was prepared from commercially available (*S*)-glycidol following the literature procedure,[18] and was treated with (*S*,*S*)-**3** to give olefin **23** (48%, Scheme 5). Once again, due to the presence of the THP groups, the diastereomeric ratio could not be ascertained at this point. Dihydroxylation followed by oxidative cleavage provided dihydroxy ketone **24** in excellent yield (85%). One-pot deprotection and subsequent spirocyclization were accomplished by treatment with DOWEX 50WX8-400 resin in methanol. Careful chromatography afforded the C_2-symmetric spiroketal **25** (58%), accompanied by three other diastereoisomers (two inseparable) which could not be identified (25% combined). The stereochemistry of the spirocenter in **25** was assigned by analogy with that observed in the spirocyclization of a number of closely related compounds,[16−20] and is supported by the fact that the signal for the hydroxyl protons in the ^{1}H NMR spectrum appears at δ 4−4.3 ppm, which has been shown to be diagnostic for an axial hydroxyl proton in related systems.[20]

This study further expands the utility of pinene-derived compounds in asymmetric synthesis. The direct conversion of aldehydes into highly enantiomerically enriched C_2-symmetric 3-methylenepentane-1,5-diols, supported by the desymmetrization procedure developed, should be of considerable application in organic synthesis. To demonstrate the utility of this method, we have synthesized the AB fragment of the spongistatin nucleus and have completed a formal total synthesis of both enantiomers of 1,7-dioxaspiro[5.5]undecane.

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Experimental Section

All solvents were redistilled prior to use. 2,3-*O*-Isopropylidene-D-glyceraldehyde,[21] 3-(tetrahydro-2*H*-pyran-2-yl)oxypropanal (**15**),[14] and (3*R*)-4-(4-methoxybenzyloxy)-3-(tetrahydro-2*H*-pyran-2-yl)oxybutanal (**22**)[18] were prepared according to reported procedures. 1,3-Dilithio-2-methylenepropane·2TMEDA was prepared as reported[2a,5] and isolated by filtration (35−50% yield). All other reagents were purchased from commercial sources and used without further purification. Scalemic 3-methylenepentane-1,5-diols were prepared from 1,3-dilithio-2-methylenepropane·2TMEDA as reported.[2a]

Column chromatography was performed on BDH silica gel 60, 230−400 mesh ASTM. Analytical thin-layer chromatography (TLC) was perfomed on precoated glass-backed plates (Merck Kieselgel 60 F_{254}) and visualized with ultraviolet light (254 nm), vanillin, or potassium permanganate, as appropriate.

General Procedure for the Double Asymmetric Allylboration of Aldehydes using (*S*,*S*)-3 or (*R*,*R*)-3 for the Preparation of 3-Methylenepentane-1,5-diols 1a−k (Table 1). A solution of (+)-*B*-chlorodiisopinocampheylborane or (−)-*B*-chlorodiisopinocampheylborane (5.4 g, 16.8 mmol) in Et_2O (20 mL) was added to a cooled (0 °C) suspension of 1,3-dilithio-2-methylenepropane·2TMEDA (2.3 g, 7.7 mmol) in Et_2O (20 mL), and the resulting yellow solution was stirred for 3 h at this temperature, during which time a heavy white precipitate was deposited. The solvent was evaporated under reduced pressure, and the residue was dissolved in dry pentane (50 mL). The solution was filtered under an argon atmosphere, and the residue was washed with a further aliquot of pentane (50 mL). The pentane was evaporated (1 mmHg), and the resulting foam was dissolved in Et_2O (50 mL). This solution was cooled to −78 °C, the aldehyde (20.5 mmol) was added dropwise, and the reaction mixture was stirred for 3 h at this temperature. Hydrogen peroxide (27 wt %, 4 mL, 32 mmol) and aqueous NaOH (4M, 4 mL, 32 mmol) were added simultaneously, and the reaction mixture was allowed to stir for a further 18 h with slow warming to room temperature. H_2O (5 mL) was added, and the reaction mixture was extracted with Et_2O. The combined organic phase was washed with water and brine, dried ($MgSO_4$), concentrated in vacuo, and chromatographed. Full characterization data for the 3-methylenepentane-1,5-diols **1a**−**k** can be found in the Supporting Information.

Determination of Diastereomeric Ratios and Enantiomeric Excesses. To determine the diastereomeric and enantiomeric excesses of diols **1a**−**h**, they were converted into their bis-(*S*)-Mosher (MTPA) esters[8] **6** using (*R*)-Mosher chloride. Their ^{1}H NMR spectra were compared with the bis-MTPA esters of the corresponding 1:1 mixture of diols **1** and **2** (*meso*) prepared by condensation of 1,3-dilithio-2-methylenepropane with the appropriate aldehyde,[2a] and the dr and ee were determined by integration of the signals for the olefinic protons (see the Supporting Information).

(6*S*,10*S*)-(+)-6,10-Dihydroxypentadecan-8-one (7). Ozone was bubbled though a solution of diol **1e** (78 mg, 0.30 mmol) in CH_2Cl_2 (5 mL) at −78 °C until the solution turned a pale blue (ca. 15 min). The ozone generator was turned off, and O_2 was bubbled through the solution until the color had discharged (ca. 5 min). Me_2S (3 mL) and EtOH (3 mL) were added, and the reaction mixture was allowed to warm to ambient temperature and stirred for 18 h. The solvent was removed under reduced pressure, and the residue was chromatographed (1:4 EtOAc/hexanes) to afford dihydroxy ketone **7** as a white amorphous solid (75 mg, 97%): TLC R_f 0.10 (1:4 EtOAc/hexanes); $[\alpha]^{23}_D$ +45.8° (*c* 0.2, $CHCl_3$) [lit.[9] $[\alpha]^{25}_D$, (−)-(*R*,*R*) isomer, −40.4° (*c* 0.2, $CHCl_3$)]; IR ($CHCl_3$) 3552, 3008, 2958, 2931, 2860, 1699 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.09−4.02 (m, 2H), 3.17 (br s, 2H), 2.55 (d, 4H, J = 5.5 Hz), 1.49−1.28 (m, 16H), 0.87 (t, 6H, J = 6.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.5, 67.6, 50.2, 36.6, 31.7, 25.1, 22.6, 14.0 (also present from the minor diastereoisomer 50.3, 67.8); MS (CI,

(21) Schmid, C. R.; Bryant, J. D. *Org. Synth*. **1993**, *72*, 6.

NH_3) *m*/*z* 276 $(M + NH_4)^+$, 259 $(M + H)^+$; HRMS (CI, NH_3) calcd for $C_{15}H_{31}O_3$ $(M + H)^+$ 259.2273, found $(M + H)^+$ 259.2279.

(1*R*,5*R*)-6-Methyl-1-phenyl-3-methyleneheptane-1,5-diol (9): as a 3:5 mixture with **1b**; TLC R_f 0.33 (2:3 EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) 7.40−7.28 (m, 5H), 5.12 (s, 1H), 5.09 (s, 1H), 5.04 (s, 3.33H), 4.89−4.80 (m, 1H), 3.59−3.48 (m, 4.33H), 2.58−2.40 (m, 2H), 2.35−2.31 (m, 4.33H), 2.10−2.03 (m, 4.33H), 1.75−1.67 (m, 4.33H), 0.99−0.97 (m, 26H).

(6*R*)-4-(2-Hydroxy-2*R*-phenylethyl)-4-iodomethyl-6-phenyl-1,3-dioxan-2-one (11). *n*-BuLi (2.4 M in hexanes, 0.5 mL, 1.2 mmol) was added to a solution of (1*R*,5*R*)-**1a** (140 mg, 0.52 mmol) in THF (10 mL), and after 1 h at room temperature CO_2 was bubbled through the solution for 1 min, a solution of I_2 (400 mg, 1.57 mmol) in THF (5 mL) was added, and the mixture was stirred for 18 h at room temperature. The solution was poured into water and extracted with Et_2O. The combined organic phase was washed with water, dried ($MgSO_4$), concentrated under reduced pressure, and chromatographed (1:4 EtOAc/hexanes) to give **11** as a clear oil (138 mg, 61% as a 1:1 mixture of diastereoisomers): TLC R_f 0.4 (2:3 EtOAc/hexanes); IR (film) 3442, 3062, 3031, 2956, 2927, 2871, 1739 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45−7.35 (m, 10H), 5.65−5.45 (m, 1H), 5.16−5.06 (m, 1H), 4.10−3.45 (m, 3H), 2.87−2.10 (m, 4H); MS (CI, NH_3) *m*/*z* 471 $(M + H - H_2O)^+$, 453 $(M + H - 2H_2O)^+$.

(1*R*,5*R*)-(+)-5-(*tert*-Butyldimethylsily)oxy-1,5-diphenyl-3-methylene-1-pentanol (12). A solution of iodocarbonate **11** (99 mg, 0.23 mmol), imidazole (25 mg, 0.37 mmol), and *tert*-butyldimethylsilyl chloride (50 mg, 0.33 mmol) in DMF (1 mL) was stirred at room temperature for 18 h. H_2O was added (10 mL) and the solution extracted with Et_2O. The ethereal extracts were washed with dilute HCl, water, and brine, dried ($MgSO_4$), evaporated, and chromatographed to yield the intermediate silyl carbonate. This was dissolved directly in glacial AcOH (3 mL) and stirred vigorously while zinc dust was added (50 mg, 0.76 mmol). After 0.5 h saturated aqueous $NaHCO_3$ was added until effervescence ceased, and the mixture extracted with Et_2O. The combined extracts were washed with H_2O, dried, concentrated, and chromatographed on silica gel (1:19 EtOAc/hexanes) to give alcohol **12** (35 mg, 40%): TLC R_f 0.43 (1:4 EtOAc/hexanes); $[\alpha]^{23}_D$ +48.1° (*c* 1.65, $CHCl_3$); IR ($CHCl_3$) 3422, 3065, 3029, 2953, 2929, 2887, 2857, 1643 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38−7.30 (m, 10H), 5.02 (s, 1H), 5.00 (s, 1H), 4.81−4.78 (m, 2H), 2.60−2.40 (m, 4H), 2.25 (br s, 1H), 0.89 (s, 9H), 0.03 (s, 3H), −0.15 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.1, 144.1, 142.7, 128.4, 128.1, 127.5, 127.2, 126.0, 125.8, 116.7, 74.5, 71.5, 47.1, 47.0, 25.9, 18.3, −4.6, −4.9 (also present from the minor diastereoisomer 143.2, 116.2, 47.5); MS (CI, NH_3) *m*/*z* 383 $(M + H)^+$; HRMS (CI, NH_3) calcd for $C_{24}H_{35}O_2Si$ $(M + H)^+$ 383.2403, found $(M + NH_4)^+$ 383.2403. Anal. Calcd for $C_{24}H_{35}O_2Si$: C, 75.34; H, 8.96. Found: C, 75.20; H, 8.82.

(1*R*,5*R*)-(+)-1,5-Di[(*tert*-butyloxy)carbonyloxy]-1,5-diphenyl-3-methylenepentane (13). To a solution of **1a** (350 mg, 1.31 mmol) in THF (3.5 mL) at 0 °C was added dropwise a solution of *n*-BuLi (2.4 M in hexanes, 1.5 mL, 3.6 mmol), and the mixture was stirred for 30 min. A solution of 2-(*tert*-butoxycarbonylimino)-2-phenylacetonitrile (BOC−ON) (890 mg, 3.6 mmol) in THF (5 mL) was added, and the mixture was warmed to room temperature and stirred for 18 h. The solution was poured into aqueous NaOH (0.4M, 30 mL) and extracted with Et_2O. The ether layer was washed with brine, and the aqueous phase was back-extracted with Et_2O. The combined organic phase was dried ($MgSO_4$), concentrated under reduced pressure, and chromatographed (1:19 EtOAc/hexanes), furnishing dicarbonate **13** as an off-white solid (460 mg, 75%): mp 79−80 °C; TLC R_f 0.46 (1:4 EtOAc/hexanes); $[\alpha]^{23}_D$ +35.7° (*c* 0.8, $CHCl_3$); IR ($CHCl_3$) 2987, 1738 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35−7.30 (m, 10H), 5.72−5.62 (m, 2H), 4.91 (s, 2H), 2.65−2.40 (m, 4H), 1.45 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.9, 140.1, 132.9, 128.5, 128.0, 126.4, 117.1, 82.1, 65.9, 43.2, 27.8 (also present from the minor diastereoisomer 129.3, 127.5, 27.7); HRMS (CI, NH_3) calcd for $C_{28}H_{40}NO_6$ $(M + NH_4)^+$ 486.2856, found $(M + NH_4)^+$ 486.2846. Anal. Calcd for $C_{28}H_{36}O_6$: C, 71.77; H, 7.74. Found: C, 71.85; H, 7.73.

(4*S*,6*R*)-4-[(2-*tert*-Butyloxy)carbonyloxy)-(2*R*)-phenethyl]-4-iodomethyl-6-phenyl-1,3-dioxan-2-one (14). IBr (1.0 M in CH_2Cl_2, 0.3 mL, 0.3 mmol) was slowly added to a solution of dicarbonate **13** (100 mg, 0.21 mmol) in PhMe (5 mL) at −80 to −85 °C (CO_2−Et_2O bath), and the mixture was stirred at this temperature for 4 h. A mixture of aqueous $NaHCO_3$ and $Na_2S_2O_3$ was added, the solution was allowed to warm to room temperature and extracted with Et_2O. The combined organic phase was washed with H_2O, dried, evaporated under reduced pressure, and chromatographed (1:9 Et_2O/pentane) to furnish iodolactone **14** as an off-white foam (93 mg, 82%): TLC R_f 0.25 (1:4 EtOAc/hexanes); $[\alpha]^{23}_D$ +0.75° (*c* 6.7, $CHCl_3$); IR ($CHCl_3$) 3033, 2978, 2930, 2856, 1746 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45−7.35 (m, 10H), 5.43 (dd, 1H, *J* = 11.9, 2.9 Hz), 5.43 (dd, 1H, *J* = 11.9, 2.9 Hz), 3.50 (d, 1H, *J* = 10.9 Hz), 3.42 (d, 1H, *J* = 10.9 Hz), 2.78 (dd, 1H *J* = 15.2, 8.6 Hz), 2.49 (m, 2H), 2.24 (dd, 1H, *J* = 14.5, 12.2 Hz), 1.47 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.4, 148.3, 139.8, 137.0, 129.1, 129.0, 128.7, 126.2, 125.7, 83.2, 81.3, 76.7, 74.2, 44.1, 39.7, 27.7, 13.8; MS (CI, NH_3) *m*/*z* 556 $(M + NH_4)^+$; HRMS (CI, NH_3) calcd for $C_{24}H_{31}INO_6$ $(M + NH_4)^+$ 556.1196, found $(M + NH_4)^+$ 556.1216. Anal. Calcd for $C_{24}H_{27}IO_6$: C, 53.54; H, 5.06. Found: C, 53.60; H, 4.88.

(3*R*,7*R*)-1,9-Di[(tetrahydropyran-2-yl)oxy]-5-methylenenonane-3,7-diol (16). Following the general procedure for double asymmetric allylboration using (*S*,*S*)-**3** and **15**[14] gave **16** as a colorless oil (45% as an inseparable mixture of diastereoisomers (ratio not determined)): TLC R_f 0.08 (2:3 EtOAc/hexanes); IR (film) 3428, 3073, 2940, 2872, 1643 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.97 (s, 2H), 4.59 (m, 2H), 4.00−3.80 (m, 6H), 3.65−3.43 (m, 4H), 3.32 (br s, 2H), 2.30−2.15 (m, 4H), 1.85−1.50 (m, 16H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.7, 115.2, 99.1, 99.0, 68.9, 68.8, 68.5, 68.5, 65.9, 65.8, 62.6, 62.3, 44.1, 36.4, 30.7, 30.5, 25.3, 19.6, 19.5; MS (CI, NH_3) *m*/*z* 388 $(M + NH_4)^+$, 373 $(M + H)^+$; HRMS (CI, NH_3) calcd for $C_{20}H_{37}O_6$ $(M + H)^+$ 373.2590, found $(M + H)^+$ 373.2592. Anal. Calcd for $C_{20}H_{36}O_6$: C, 64.49; H, 9.74. Found: C, 64.68; H, 9.89.

(3*S*,7*S*)-3,7-Dihydroxy-1,9-di[(tetrahydropyran-2-yl)-oxy]nonan-5-one (17). From **16** (300 mg, 0.81 mmol) the procedure described for **7** gave **17** as a colorless oil (295 mg, 97%): TLC R_f 0.32 (1:24 MeOH/$CHCl_3$); IR (film) 3427, 3008, 2944, 2875, 1708 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.48 (br s, 2H), 4.23−4.15 (m, 2H), 3.87−3.71 (m, 4H), 3.53−3.41 (m, 6H), 2.63−2.47 (m, 4H), 1.76−1.42 (m, 16H); ^{1}H NMR (300 MHz, CD_3OD) δ 4.61 (br s, 2H), 4.25 (m, 2H), 3.92−3.84 (m, 4H), 3.48−3.58 (m, 4H), 3.33 (m, 2H), 2.66 (s, 4H), 1.86−1.54 (m, 16H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.8, 210.7, 210.7, 99.0, 99.0, 66.3, 66.1, 64.9, 64.8, 62.5, 62.3, 50.5, 36.2, 30.6, 30.5, 25.3, 19.6, 19.5; MS (CI, NH_3) *m*/*z* 392 $(M + NH_4)^+$; HRMS (CI, NH_3) calcd for $C_{19}H_{38}NO_7$ $(M + NH_4)^+$ 392.2648, found $(M + NH_4)^+$ 392.2654. Anal. Calcd for $C_{19}H_{34}O_7$: C, 60.94; H, 9.15. Found: C, 61.00; H, 9.26.

(4*S*,6*S*,10*S*)-(+)-1,7-Dioxaspiro[5.5]undecan-4,10-diol (18).[13] A solution of ketone **17** (795 mg, 2.13 mmol) in MeOH (10 mL) was stirred at room temperature with freshly washed DOWEX 50WX8-400 resin (50 mg) for 18 h. The mixture was filtered, and the resin was washed with further MeOH. The combined organic phase was concentrated to give a solid residue. Chromatography (1:19 MeOH/$CHCl_3$) gave first an unidentified mixture of products, followed by spiroketal **18** as a white solid (300 mg, 75%): mp 119−120 °C (Me_2CO) (lit.[13] mp 153−154 °C); TLC R_f 0.07 (1:19 MeOH/$CHCl_3$); $[\alpha]^{23}_D$ +124.5° (*c* 0.4, Me_2CO) (lit.[13] $[\alpha]_D$ +121.4° (*c* 0.5, Me_2CO)); IR ($CHCl_3$) 3376, 2951, 2879 cm^{-1}; ^{1}H NMR (300 MHz, $(CD_3)_2$-CO) δ 4.00−3.90 (m, 2H), 3.74 (m, 2H), 3.63−3.53 (m, 4H), 1.98−1.91 (m, 2H), 1.85−1.77 (m, 2H), 1.45−1.22 (m, 4H); ^{1}H NMR (300 MHz, CD_3OD) δ 4.03−3.92 (m, 2H), 3.69−3.55 (m, 6H), 2.02−1.95 (m, 2H), 1.88−1.82 (m, 2H), 1.51−1.27 (m, 4H); ^{13}C NMR (75 MHz, $(CD_3)_2CO$) δ 99.0, 63.2, 58.5, 45.3, 35.2;

MS (CI, NH_3) *m*/*z* 206 $(M + NH_4)^+$, 189 $(M + H)^+$; HRMS (CI, NH_3) calcd for $C_9H_{17}O_4$ $(M+H)^+$ 189.1123, found $(M + H)^+$ 189.1127.

(2*R*,4*R*,8*R*,10*R*)-1,11-Di(4-methoxybenzyloxy)-2,10-di-[(tetrahydropyran-2-yl)oxy]-6-methyleneundecane-4,8-diol (23). Following the general procedure for double asymmetric allylboration using (*S*,*S*)-**3** and **22**[18] gave **23** as a colorless oil (48% as an inseparable mixture of diastereoisomers (ratio not determined)): TLC R_f 0.06 (2:3 EtOAc/hexanes); $[\alpha]^{23}_D$ +4.1° (*c* 3.9, $CHCl_3$); IR (film) 3423, 3071, 2972, 2854, 1642 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.24 (m, 4H), 6.88 (m, 4H), 4.96 (m, 2H), 4.74 (m, 2H), 4.51−4.45 (m, 4H), 4.15−3.92 (m, 6H), 3.83 (s, 3H), 3.81 (s, 3H), 3.71−3.41 (m, 8H), 2.25−2.20 (m, 4H), 1.87−1.45 (m, 16H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.2, 143.7, 130.4, 130.2, 130.2, 129.4, 129.2, 115.0, 113.8, 99.9, 99.5, 99.3, 99.2, 99.0, 76.6, 76.2, 75.8, 75.4, 75.3, 72.9, 72.5, 72.4, 69.4, 68.8, 67.9, 67.4, 65.9, 64.4, 64.2, 62.7, 55.3, 44.7, 44.4, 44.1, 43.7, 39.1, 39.0, 31.2, 25.4, 25.2, 25.2, 20.9, 20.8, 19.7; MS (Electrospray) *m*/*z* 690.2 $(M + H_2O)^+$, 673.1 $(M + H)^+$; Anal. Calcd for $C_{38}H_{56}O_{10}$: C, 67.83; H, 8.39. Found: C, 67.72; H, 8.41.

(2*R*,4*S*,8*S*,10*R*)-4,8-Dihydroxy-1,11-di(4-methoxybenzyloxy)-2,10-di[(tetrahydropyran-2-yl)oxy]undecan-6-one (24). A solution of OsO_4 (4 wt % in H_2O, 2 mL) was added to alkene **23** (1.07 g, 1.6 mmol) and NMO (380 mg, 3.2 mmol) in *t*-BuOH/THF/H_2O (42 mL, 10:3:1) at room temperature, and the reaction mixture was stirred for 72 h, during which time the color faded from dark brown to pale yellow. To this solution were added H_2O (10 mL) and $NaIO_4$ (1.08 g, 5.05 mmol), and the mixture was stirred for 20 h at room temperature. The mixture was filtered and extracted with Et_2O (100 mL), and the aqueous phase was treated with saturated aqueous $Na_2S_2O_3$ (50 mL) and concentrated in vacuo to about half-volume. The mixture was extracted with Et_2O (2 × 50 mL) and CH_2Cl_2 (2 × 50 mL), and the combined organic extracts were washed with H_2O and brine, dried, concentrated, and chromatographed (2:3 EtOAc/hexanes and then 1:99 MeOH/$CHCl_3$) to give **24** as a clear oil (0.92 g, 85%): TLC R_f 0.55 (1:99 MeOH/$CHCl_3$); IR (film) 3480, 2945, 2856, 1709 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.24 (m, 4H), 6.84 (m, 4H), 4.47 (m, 2H), 4.52−4.44 (m, 4H), 4.43−3.89 (m, 6H), 3.78 (s, 3H), 3.77 (s, 3H), 3.66−3.42 (m, 8H), 2.67−2.46 (m, 4H), 1.78−1.42 (m, 16H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.4, 210.3, 159.2, 130.3, 130.2, 130.2, 129.4, 129.2, 113.8, 113.8, 99.7, 99.5, 99.0, 98.9, 77.4, 75.6, 75.3, 75.0, 74.8, 73.0, 72.4, 72.3, 67.2, 66.9, 65.8, 65.5, 64.5, 64.3, 62.7, 60.6, 55.2, 51.1, 50.8, 50.7, 50.5, 39.0, 38.8, 38.7, 31.3, 31.1, 25.4, 25.2, 21.0, 20.9, 20.8, 19.7; MS (electrospray) *m*/*z* 697.2 $(M + Na)^+$. Anal. Calcd for $C_{37}H_{54}O_{11}$: C, 65.85; H, 8.07. Found: C, 65.97; H, 8.15.

(2*R*,4*S*,6*R*,8*R*,10*S*)-2,8-Di(4-methoxybenzyloxymethyl)-1,7-dioxaspiro[5.5]undecan-4,10-diol (25). From **24** (650 mg, 0.96 mmol) the procedure described for **18** gave **25** as a pale yellow oil (271 mg, 58%): TLC R_f 0.22 (3:2 EtOAc/hexanes); $[\alpha]^{23}_D$ −21.5° (*c* 3.0, $CHCl_3$); IR (film) 3523, 2930, 2861 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.24 (d, 4H, J = 8.6 Hz), 6.86 (d, 4H, J = 8.6 Hz), 4.51−4.48 (m, 4H), 4.34−4.29 (m, 2H), 4.30−4.00 (br s, D_2O exchange, 2H), 4.15−4.05 (m, 2H), 3.78 (s, 6H), 3.45−3.42 (m, 4H), 1.93−1.85 (m, 2H), 1.75−1.63 (m, 4H), 1.54−1.44 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.2, 130.2, 129.2, 113.8, 100.1, 72.8, 72.4, 64.3, 55.2, 39.4, 33.7; MS (CI, NH_3) *m*/*z* 506 $(M + NH_4)^+$, 489 $(M + H)^+$; HRMS (CI, NH_3) calcd for $C_{27}H_{40}NO_8$ $(M + NH_4)^+$ 506.2754, found $(M + NH_4)^+$ 506.2765.

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Supporting Information Available: Spectral data for 3-methylenepentane-1,5-diols **1a**−**k**, copies of ^1H NMR and ^{13}C NMR spectra of diols **1b**, **1c**, **1d**, **9** (^1H NMR only, as a mixture with **1b**), iodocarbonate **11**, and spiroketals **18** and **25**, ^1H NMR spectra of bis-Mosher esters derived from diols **1a**−**h**, NOE measurements on iodocarbonate **14**, and X-ray crystallographic data for Mosher ester **6g**. This material is available free of charge via the Internet at http://pubs.acs.org.

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