J. Org. Chem. 1984, *49*, 2513–2516

79%) of **8** provided **9**, which was converted into the labile aldehyde **10** in 80–85% overall yield by sequential protection of the free hydroxyl as the *tert*-butyldimethylsilyl ether[18] and reduction [(a) t-BuMe$_2$SiCl/imidazole/DMF, 7 h, room temperature; (b) DIBAL (1.8 equiv, 1.0 N in PhMe)/CH$_2$Cl$_2$, −90 °C, 1 h]. For elaboration of the remaining two chiral centers present at C(3) and C(12) in **4**, the aldehyde **10** was treated with crotyl bromide in the presence of Cr(II)[19] [CrCl$_2$/CH$_3$CH=CHCH$_2$Br/THF, 0 °C → room temperature, 2 h] which proceeded without a significant degree of stereoselectivity to give the pair of homoallylic alcohols **11** and **12** in an approximately 1:1.5 ratio (70–75%). These diastereomeric alcohols were readily separated by HPLC, and the *tert*-butyldimethylsilyl (TBS) hydroxyl protecting group of **11** was smoothly removed (5.0 equiv, 1 N n-Bu$_4$NF/THF, room temperature, 15 min; 95%) to give the unsaturated diol **13**. When the furan ring of **13** was oxidized[14] (1.05 equiv of MCPBA/NaOAc/CH$_2$Cl$_2$, −23 °C, 1 h) and the resulting crude mixture of hydropyranones was treated with aqueous acid [2.4 N HI/KI, H$_2$O–CH$_3$CN (2.5:1), 0 °C, 50 min], the 2,9-dioxabicyclo[3.3.1]nonane **14** was isolated in 77% yield. Oxidative cleavage of the terminal double bond [1.0 equiv of O$_3$, CH$_3$OH/CH$_2$Cl$_2$ (1:10), −78 °C, 15 min; Ph$_3$P, 0 °C, 15 min) afforded the unstable aldehyde **15**. Wittig olefination of crude **15** with purified (α-carbethoxyethylidene)triphenylphosphorane (benzene, 80 °C, 15 h) afforded the unsaturated ester **4** in 41% overall yield from **14**. The **4** thus obtained gave spectra [NMR and IR and optical rotation ($[\alpha]^{\rm rt}_{\rm D}$ −185.2° (*c* 1.1, CHCl$_3$), lit.[8] $[\alpha]^{\rm rt}_{\rm D}$ −186.3° (*c* 1.085, CHCl$_3$)] that were identical with those obtained independently by Ireland for a sample of **4** prepared from D-glucose. Since **4** has been converted in five steps into tirandamycic acid,[8] the sequence described above constitutes a concise (nine steps from **6**), formal asymmetric synthesis of this substance.

Acknowledgment. We thank the National Institutes of Health (GM 31077) and the Robert A. Welch Foundation for their generous support of this research. We are grateful to Professor R. E. Ireland for providing us with experimental details for the conversion of **15** to **4** as well as the necessary spectral data for comparison and also to Professor D. A. Evans for supplying experimental details for the preparation and use of the chiral boron enolate derived from **7**.

Registry No. **2**, 34429-71-5; **4**, 78686-73-4; **5**, 14920-89-9; **6**, 52480-43-0; **7** ((*Z*)-dibutylboryl enolate), 87758-64-3; **8**, 90432-93-2; **9**, 90528-03-3; **9** (TBS ether), 90432-94-3; **10**, 90432-95-4; **11**, 90432-96-5; **12**, 90528-04-4; **13**, 90432-97-6; **14**, 90432-98-7; **15**, 78686-72-3; CH$_3$CH=CHCH$_2$Br, 4784-77-4; (α-carbethoxyethylidene)triphenylphosphorane, 5717-37-3.

Supplementary Material Available: Experimental procedures and data for the intermediates **10–15** in this study (4 pages). Ordering information is given on any current masthead page.

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[19] Hiyama, T.; Okude, Y.; Kimura, K.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 561.

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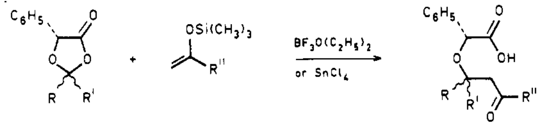
Enantioselective Syntheses of Aldols and Homoallylic Alcohols from 1,3-Dioxolan-4-ones Using Mandelic Acid as Chiral Auxiliary

Summary: The 1,3-dioxolan-4-ones obtained by condensation of (*S*)-(+)- or (*R*)-(−)-mandelic acid with aldehydes and ketones react under electrophilic conditions cleanly and with reasonable diastereoselectivities with enol silyl ethers or allylsilanes. The chiral auxiliary can be removed with Pb(OAc)$_4$ followed by acid hydrolysis to furnish without racemization the aldols or homoallylic alcohols.

Sir: The search continues unabatedly for new enantio- and/or diastereoselective carbon–carbon bond forming reactions.[1] Asymmetric aldol and related condensations form a central part of these efforts.[2] The major approach has been the use of chiral nucleophiles such as enolates wherein the chirality stems from the presence of a chiral auxiliary.[3,4] In contrast examples of the reaction of achiral anion precursors with electrophilic equivalents provided with a chiral auxiliary are few. Notable successes in this approach have been achieved, however, by Johnson and Kishi, who have employed, as electrophilic components, chiral cyclic acetals derived by the condensation of chiral 1,2- and 1,3-diols with the carbonyl acceptors.[5] These are condensed with various achiral carbanion equivalents in the presence of Lewis acids. The diastereoselectivities are good to excellent but the cost of the diols and the removal of the auxiliary form limitations.[5]

In connection with other work,[6] it occurred to us that 1,3-dioxolan-4-ones **1** might fulfill a similar purpose. We expected, and this was borne out in fact, that carboxylate would be the better leaving group in the reaction of **1**, illustrated with (*R*)-(−)-mandelic acid, with enol silyl ethers (eq 1).



1 2 (1)

The derivatives **1** were obtained as cis,trans mixtures by condensation of commercial (*R*)-(−)- or (*S*)-(+)-mandelic acids with aldehydes and ketones following literature procedures.[7] For **1a–d** the major isomer (cis) was isolated in >99% purity by recrystallization from hexane or hexane/ethanol. Compound **1e** was separated into its cis and trans isomers by chromatography over SiO$_2$ with hexane–

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[1] (a) Valentine, D., Jr.; Scott, J. W. *Synthesis* **1978**, 329. (b) Bartlett, P. A. *Tetrahedron* **1980**, *3*, 36. (c) "Asymmetric Reactions and Processes in Chemistry"; Eliel, E. L., Otsuka, S., Eds.; American Chemical Society: Washington, DC, 1982.

[2] (a) Mukaiyama, T. *Org. React.* (*N.Y.*) **1982**, *28*, 203. (b) Meyers, A. I. *Pure Appl. Chem.* **1979**, *55*, 1255. (c) Heathcock, C. H. *Science* (*Washington, D.C.*) **1981**, *214*, 395.

[3] (a) Masamune, S.; Ellingboe, J. W.; Choy, W. *J. Am. Chem. Soc.* **1982**, *104*, 5526. (b) Evans, D. A.; Nelson, J. V.; Taber, T. R., *Top. Stereochem.* **1982**, *13*, 1. (c) Enders, D.; Eichenauer, H. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 397.

[4] For asymmetric aldol condensations using chiral amines, see: Mukaiyama, T.; Iwasawa, N. *Chem. Lett.* **1982**, 1903; **1983**, 297.

[5] (a) Elliott, J. D.; Choi, V. M. F.; Johnson, W. S. *J. Org. Chem.* **1983**, *48*, 2293. (b) Bartlett, P. A.; Johnson, W. S.; Elliott, J. D. *J. Am. Chem. Soc.* **1983**, *105*, 2088 and previous papers. (c) McNamara, J. M.; Kishi, Y. *Ibid.* **1982**, *104*, 7371. See also: (d) Mukaiyama, T.; Narasaka, K.; Bunno, K. *Chem. Lett.* **1973**, 1011. (e) Murata, S.; Suzuki, M.; Noyori, R. *J. Am. Chem. Soc.* **1980**, *102*, 3248. (f) Nakamura, E.; Horiguchi, Y.; Shimada, J.-i.; Kuwajima, I. *J. Chem. Soc., Chem. Commun.* **1983**, 796.

[6] Mashraqui, S. H.; Kellogg, R. M. *J. Am. Chem. Soc.* **1983**, *105*, 7792.

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Table I. Condensation of 1,3-Dioxolan-4-ones with Enol Silyl Ethers and Allylsilane[a,b]

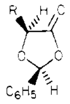
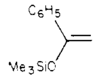
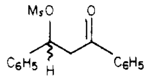
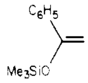
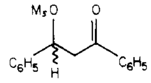
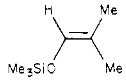
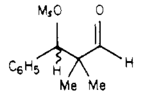
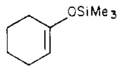
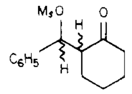
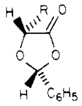
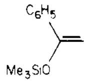
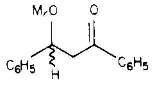
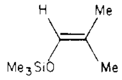
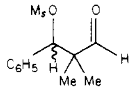
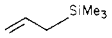
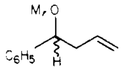
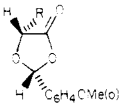
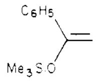
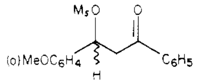
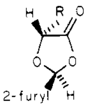
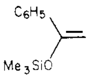
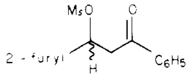
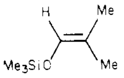
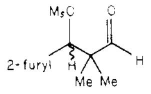
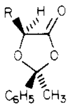
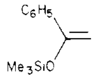
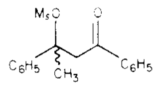
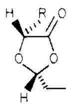
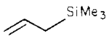
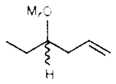
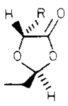
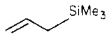
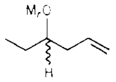
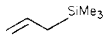
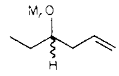
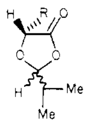
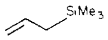
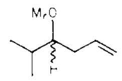
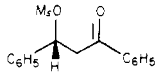
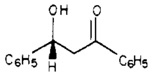
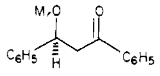
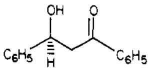
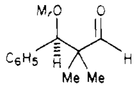
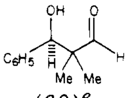
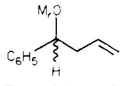
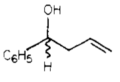
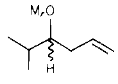
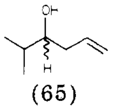
entry	1,3-dioxolan-4-ones[c] (R = C$_6$H$_5$)	silyl reagents	products[f]	yields,[d] %	diastereomeric[e] ratio
1	 *cis*-(2*S*,5*S*)-1a			98	93.5(M$_s$*R*):6.5(M$_s$*S*)
2	*cis*-(2*S*,5*S*)-1a/ *trans*-(2*R*,5*S*)-1a (65:35)			96	64(M$_s$*R*):36(M$_s$*S*)
3	*cis*-(2*S*,5*S*)-1a			95	91(M$_s$*R*):9(M$_s$*S*)
4	*cis*-(2*S*,5*S*)-1a			90[g]	49:23:17:11[h]
5	 *cis*-(2*R*,5*R*)-1a			96	83(M$_r$*S*):17(M$_r$*R*)
6	*cis*-(2*R*,5*R*)-1a			96	93(M$_r$*S*):7(M$_r$*R*)
7	*cis*-(2*R*,5*R*)-1a			84	64(M$_r$*S*):36(M$_r$*R*)
8	 *cis*-(2*R*,5*R*)-1b			95	75(M$_r$*S*):25(M$_r$*R*)
9	 *cis*-(2*S*,5*S*)-1c			76[g]	71.5(M$_s$*R*):28.5(M$_s$*S*)[i]
10	*cis*-(2*S*,5*S*)-1c			90[g]	82.5(M$_s$*R*):17.5(M$_s$*S*)[i]
11	 (2*S*,5*S*)-1d			65[g]	63(M$_s$*R*):37(M$_s$*S*)[j]
12	 *cis*-(2*R*,5*R*)-1e			50–57	72(M$_r$*S*):28(M$_r$*R*)
13	 *trans*-(2*S*,5*R*)-1e			50–57	75(M$_r$*S*):25(M$_r$*R*)
14	*cis*-(2*R*,5*R*)-1e/ *trans*-(2*S*,5*R*)-1e (64:36)			50–57	70(M$_r$*S*):30(M$_r$*R*)
15	 *cis*-(2*R*,5*R*)-1f/ *trans*-(2*S*,5*R*)-1f (81.5:18.5)			47	81.5(M$_r$*S*):18.5(M$_r$*R*)

Table I (*Continued*)

[a] For the entries 1-11 1 0.1 M solution of 1,3-dioxolan-4-one in CH_2Cl_2 containing 1.5-2 molar equiv of appropriate silyl reagent was cooled to −80 °C and 0.5 equiv of $BF_3 \cdot O(C_2H_5)_2$ was introduced by syringe. The clear solution was warmed to −35 °C for 3-4 h, quenched with aqueous NH_4Cl, and worked up in ether. [b] For the entries 12-15, the 1,3-dioxolan-4-one was treated with neat allylsilane in the presence of 2.5 equiv of anhydrous $ZnBr_2$ at 70-100 °C for 3 h, and the reaction was quenched with aqueous NH_4Cl, and worked up as usual. [c] Configuration and cis/trans ratio determined by ^1H NMR. [d] Isolated yields unless mentioned otherwise. [e] Determined by ^1H NMR and/or analytical HPLC. [f] M refers to mandelic acid residue (see eq 1, structure 2). Subscript gives configuration of mandelic acid used. [g] Yield based on ^1H NMR. [h] Stereochemistry not assigned. [i] Configuration at C-2 assumed by analogy with 1a. [j] Assignment only tentative.

Table II. Removal of Chiral Auxiliary from the Condensed Products[a]

diastereomer (config)[b]	product (yield, %)[c]	$[\alpha]_D^{25}$	ee, %	config	ref
 *S,R* (>99%)	 (60)[d]	+31.97° (*c* 0.76, MeOH)	>98	*R*	15
 *R,S* (>99%)	 (60)[d]	−32.50° (*c* 0.4, MeOH)	>98	*S*	15
 *R,S* (>99%)	 (60)[e]	−32.46° (*c* 0.81, $CHCl_3$)	>98	*S*[f]	16
 *R,S*:*R,R* (89.5/10.5)	 (50)	−40.5° (*c* 0.88, C_6H_6)	~78	*S*	17
 *R,S*:*R,R* (81.5/18.5)	 (65)	−2.3° (*c* 4.7, C_6H_6)	63	*S*	17

[a] To a 1 mmol solution of the substrate in ethyl acetate-ether (1:4, 20 mL) was added portionwise slightly less than 1 equiv of freshly crystallized $Pb(OAc)_4$. After being stirred for 30-45 min, the reaction mixture was diluted with THF and 1 N HCl was added. The reaction mixture was vigorously stirred at ambient temperature for 1-3 h (TLC monitoring) and worked up in ether. [b] First letter gives configuration of mandelic acid residue, second that of new asymmetric center. M stands for mandelic moiety. [c] Isolated yields unless otherwise designated. [d] About 5% dehydration product is formed. [e] A less polar component, not identified, is also formed. [f] Optical purity and absolute configuration were determined by converting it to the corresponding known diol with $LiAlH_4$, $[\alpha]_D^{25}$ −28.0° (*c* 1, C_6H_6) (lit.[16] $[\alpha]_D^{25}$ −26.7° (*c* 1, C_6H_6)), for the *S* configuration.

CH_2Cl_2 (1:1) as eluant.[8] Compound **1f** could not be separated readily.

The 1,3-dioxolones of aromatic aldehydes and that of acetophenone (**1d**) in the presence of $BF_3 \cdot O(C_2H_5)_2$[9] react smoothly in CH_2Cl_2 solution with silyl enol ether or allyl silane[10] at low temperatures (−80 to −30 °C over 3.5 h) to provide two diastereomeric *acids*. Acidification followed by extraction leads to the products in good yields. The results are listed in Table I. Diastereomeric ratios were determined by HPLC and ^1H NMR (200 MHz) spectral analysis.[11] For entries 1, 2, and 5–7, the pure major diastereomers were readily isolated by flash chromatography over SiO_2 ($CHCl_3$ with 1–10% CH_3OH). Effective separation methods for the remaining diastereomers have not yet been developed although initial attempts led to partial separation for the case of entry 15.

The dioxolones from aliphatic aldehydes (entries 12–15) are much less reactive and are recovered unchanged on reaction with enol silyl ethers under a variety of conditions.[12] With trimethylallylsilane in the presence of $BF_3 \cdot O(C_2H_5)_2$ reaction did occur at ambient temperature but only in 15–25% yield. Acceptable results, however, were obtained with anhydrous $ZnBr_2$ with neat allylsilane at 70–100 °C for 3 h. This procedure has recently been described by Kozikowski for another application.[13]

The chiral auxiliary appendage can be removed *without detectable racemization of the newly created chiral center* by oxidative decarboxylation[14] using slightly less than 1 equiv of freshly crystallized $Pb(OAc)_4$ in ethyl acetate:ether

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(8) The cis isomers of this five membered heterocycle are thermodynamically the most stable. This point has been established by various NMR studies. See, for example: (a) Pilgram, K.; Zapan, M. *J. Heterocycl. Chem.* **1977**, *14*, 1035. (b) Frater, G.; Müller, U.; Günther, W. *Tetrahedron Lett.* **1981**, *22*, 4221. (c) Seebach, D.; Naef, R. *Helv. Chim. Acta* **1981**, *64*, 2764. There is a good precedent for this phenomenon in five-membered rings and the basis for assignment of stereochemistry from NMR shifts seems quite sound (confirmed also by NOE experiments). See, for example: (d) Huisgen, R.; Scheer, W.; Szeimies, G.; Huber, H. *Tetrahedron Lett.* **1966**, 397. (e) Huisgen, R.; Scheer, W.; Huber, H., *J. Am. Chem. Soc.* **1967**, *69*, 1753.

(9) $SnCl_4$ can also be used but diastereoselectivities are generally lower.

(10) For applications of allyl silanes in organic synthesis, see: Sakurai, H. *Pure Appl. Chem.* **1982**, *54*, 1.

(11) Spectral data for all new compounds and key intermediates described herein are given as supplementary material. See paragraph at end of paper.

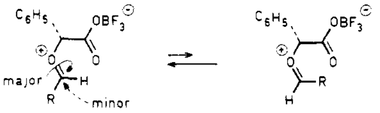
(12) $BF_3 \cdot O(C_2H_5)_2$ in CH_2Cl_2 from −80 °C to ambient temperature over 24 h; $TiCl_4$ in CH_2Cl_2 at 0 °C for 10 h; $SnCl_4$ in CH_3CN at −20 °C to 0 °C over 18 h.

(13) Kozikowski, A. P.; Sorgi, K. L.; Wang, B. C.; Xu, Z.-b., *Tetrahedron Lett.* **1983**, *24*, 1563.

(14) Precedent exists for oxidative decarboxylation of α-alkoxy acids with $Pb(OAc)_4$. See: Kitagawa, I.; Yoshikawa, M.; Ikenishi, Y.; Im, K. S.; Yosioka, Y. *Tetrahedron Lett.* **1976**, 549.

(1:4) at room temperature for 30–45 min. By ^{1}H NMR an intermediate acetate (derived by trapping of the carbonium ion generated on oxidative decarboxylation) can be detected. In a single-pot procedure the reaction mixture was diluted with THF and 1 N HCl was added to hydrolyze the acetates. After extraction and purification by thin-layer chromatography the aldols or homoallylic alcohols were isolated. The assignments of absolute configurations are based on the literature data and chemical correlations cited in Table II. These correlations were used for the unambiguous assignments in Table I (entries 1, 5–7, and 15). Other assignments in Table I are based on analogy and the assumption of a common mechanism.

Although the pure cis isomers were often used it became clear the **1** isomerizes to cis–trans mixtures during the condensation. When a CH_2Cl_2 solution of pure *cis*-**1a** (Table I) was treated with $BF_3{\cdot}O(C_2H_5)_2$ at −80 to −40 °C for 2 h, the recovered starting material after workup consisted of cis and trans isomers in 65:35 ratio. The diastereomeric ratio of the products **2** is also nearly independent of the starting geometry of **1** for dioxolones from aliphatic aldehydes (entries 12–14, Table I). The stereochemical results in all cases are in accord with nucleophilic attack on less hindered oxonium ion **3a** predominantly trans to the phenyl substituent as illustrated for **1** derived from (*R*)-mandelic acid and an aldehyde (eq 2). However, the starting geometry of the dioxolone can be partially reflected in products **2**, at least in one case (entries 1–2); this may be the result of a minor competing mechanism.



3a 3b (2)

Acknowledgment. The Dutch National Science Foundation (Z.W.O.), administered through the Office for Chemical Research (S.O.N.), has provided a grant for S.H.M.

Supplementary Material Available: Experimental details of compounds used in this study (4 pages). Ordering information is given on any current masthead page.

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(15) Enantiomeric purity established by conversion to acetate (acetic anhydride/pyridine), $[\alpha]^{25}{}_D$ +30.50° (*c* 0.83, MeOH) (Sugasawa, T.; Toyoda, T. *Tetrahedron Lett.* **1979**, 1423, $[\alpha]^{25}{}_D$ +30.8 ± 0.2° (MeOH). The (+) enantiomer has been shown to have the *R* configuration. A single peak (>98% ee) was observed in the ^{19}F NMR spectra of the Mosher esters.

(16) Guetté, M.; Capillon, J.; Guetté, J. P. *Tetrahedron* **1973**, *29*, 3659.

(17) Absolute configurations were assigned on the basis of the following reference: Herold, T.; Schrott, U.; Hoffmann, R. W.; Schnelle, G.; Ladner, W.; Steinback, K. *Chem. Ber.* **1981**, *114*, 359. Enantiomeric purity was determined by ^{1}H NMR and/or ^{19}F NMR spectra of the corresponding Mosher esters.