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Highly Stereoselective Aldol Reaction for the Synthesis of γ-Lactones Starting from Tartaric Acid

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Received June 9, 2004

A simple stereoselective process for the synthesis of highly substituted γ-lactones was developed based on aldol reactions between the enolate of dioxanes derived from tartaric acid and aldehydes. A range of aromatic and aliphatic aldehydes were reacted, in most cases achieving good yields and stereoselectivity. The limitations of this reaction were identified and a transition state is proposed.

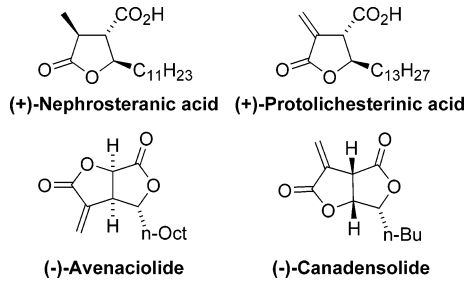
Introduction

The γ-lactonic moiety is widely dispersed in natural compounds that show a wide range of biological activities (Chart 1). The facile construction of enantiomerically pure γ-butyrolactones is thus extremely useful since it provides the chiral building blocks for the synthesis of natural products,[1] such as the paraconic acids and their structural analogues and stereoanalogues.

One of the principal difficulties encountered during their synthesis is the control of the stereogenic center at the γ carbon.[2] We present the results of a study of aldol reactions at the structurally interesting dioxane **1**[3] (Figure 1) derived from tartaric acid.

Tartaric acid is a naturally occurring inexpensive optically active compound. Through its two asymmetric carbons it can undergo diastereoselective alkylation as was shown by Seebach[4] via lithium enolates derived from dimethyl tartrate acetonide **2** (Figure 1). Evans[5] also reported that tartrate derivatives underwent highly diastereoselective aldol reactions with a variety of prochiral aldehydes and activated ketones. Berens[6] and Scharf[7] have converted dioxane **3** and its derivatives into a potential ligand for metal-mediated asymmetric catalysis. We have reported[8] the importance of the translation of the natural chirality of tartaric acid to the 2,3-butane diacetal backbone in dioxane **3** (Figure 2) and its use as a chirality memory. These trans diaxial diacetals are remarkably configurationally and probably conformationally stable. Ley[9] has also investigated 2,3-butane diacetal tartrate derivatives confirming a chiral memory protocol involved in the synthetic procedure. The 2,3-butane diacetal is also an excellent stereodirecting group for aldol reactions even when double deprotonation occurs.[3] This reaction has been reported briefly for the

CHART 1



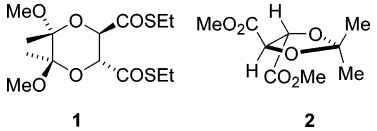


FIGURE 1. Acetals derived from tartaric acid.

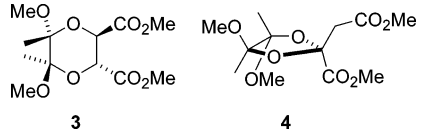


FIGURE 2. Ring contraction of dioxane **3** forms dioxolane **4**.

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(1) (a) Koch, S. S. C.; Chamberlin, A. R. *J. Org. Chem.* **1993**, *58*, 2725. (b) Chhor, R. B.; Nosse, B.; Sörgel, S.; Böhm, C.; Seitz, M.; Reiser, O. *Chem. Eur. J.* **2003**, *9*, 260.

(2) Fernandez, A. M.; Plaquevent, J. P.; Duhamel, L. *J. Org. Chem.* **1997**, *62*, 4007.

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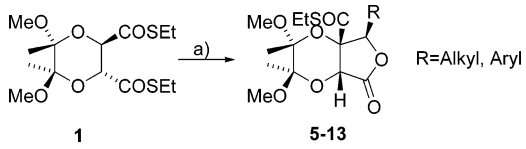
(7) Haag, D.; Runsink, J.; Scharf, H. D. *Organometallics* **1998**, *17*, 398.

(8) Barros, M. T.; Burke, A. J.; Maycock, C. D. *Tetrahedron Lett.* **1999**, *40*, 1583.

(9) (a) Dixon, D. J.; Foster, A. C.; Ley, S. V.; Reynolds, D. J. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1631. (b) Ley, S. V.; Baeschlin, D. K.; Dixon, D. J.; Foster, A. C.; Ince, S. J.; Priepke, H. W. M.; Reynolds, D. J. *Chem. Rev.* **2001**, *101*, 53.

10.1021/jo049027h CCC: $27.50
Published on Web 10/09/2004

SCHEME 1[a]



[a] Reagents and conditions: (a) LDA, THF, RCHO, −78 °C.[3]

synthesis of (+)-nephrosteranic acid[3] with use of alkyl aldehydes. A wider study of this aldol reaction with a broad range of aldehydes with a view to determining its scope and limitations is reported here.

Results and Discussion

Previous studies[8] have shown that the dioxane **3** (Figure 2), obtained from the reaction of 2,2,3,3-tetramethoxybutane[10] with tartaric acid, underwent an unexpected rearrangement upon treatment with lithium amide base to give the chiral dioxolane **4** (Figure 2).

Dithioester **1**, readily obtained by transesterification[11] of dioxane **3**, became the pivot of our studies since its enolate or dienolate did not undergo the ring contraction reaction. This is probably due to the higher stability of the enolates formed since thioesters show many characteristics of ketones due to poor orbital overlap between the sulfur atom and the carbonyl group. The formation of the dienolate may also help to prevent elimination although we believe it is in equilibrium with the monoenolate.

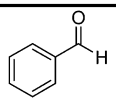
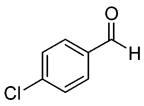
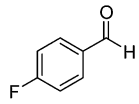
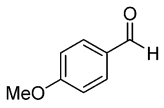
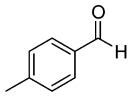
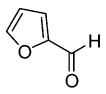
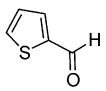
The generation of the dienolate by deprotonation of the C_2 symmetric dithioester **1** was performed with 2.2 equiv of LDA. Quenching with various aldehydes formed exclusively one of the possible diastereomeric lactones (**5**−**13**) in good yields (Scheme 1; Table 1).

In general good yields of aldol products as their lactones were formed in the yield range (60−70%). A small amount of oxidized product **14** was normally isolated. Ley[9] has reported the preparation of methyl ester **15** via oxidation of the enolate of **3** with iodine. Compound **14** became the major product (84%) when the aldol reaction was performed with 4-nitrobenzaldehyde and no aldol product was obtained (Figure 3) and 4-nitrobenzyl alcohol was recovered in about 20% yield. Pivalaldehyde also did not produce any aldol product and a small amount of oxidized product **14** (18%) was recovered along with starting material.

The assignment of the configuration (1*R*,6*R*,9*R*) for the lactone **6** was made according to the ORTEP diagram obtained from its X-ray crystal data (Figure 4). For all of the lactones (**5**−**13**), configurational assignment was made by analogy with this crystal structure, the similarity of the NMR data for these compounds, and also corroborated by the synthesis of (+)-nephrosteranic acid,[3] which was prepared by using the same reaction.

The dienolate **16**, which has been isolated as its bissilyl enol ether[3] **17**, is probably formed readily because the two enolate systems are independent due to being distorted out of coplanarity by the rigid chair conformation of the dioxane ring (Figure 5). This also reduces

TABLE 1. Aldol Reaction of Dioxane 1 with Aldehydes

Aldehyde	Product	Reaction Time (h)	Yield (%)
	**5**	2	64
	**6**	3	61
	**7**	2	60
	**8**	2	70
	**9**	2	62
	**10**	2	65
	**11**	2	66
	**12**	2	62
	**13**	2	68

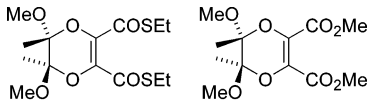


FIGURE 3. Oxidized dioxanes.

eclipsing interactions with the adjacent carboxyl group, which would occur in the monoenolate. Intramolecular complexation of the lithium ion favors the *Z,Z* (S-priority) C_2 symmetric structure and also sets the system up for stereoselective attack. A possible transition state for this stereoselective aldol reaction is indicated in Figure 5. Complexation of the enolate lithium ion with the dioxane oxygen and the carbonyl of the aldehyde, as shown in Figure 5, favors the formation of the observed products. The orientation of the aldehyde is dictated by steric interactions with the dioxane ring and favors attack at the *Si* face of the carbonyl.

Cyclization of the aldol alkoxide to form the lactone is essential to prevent the reverse aldol occurring and probably occurs because of an equilibrium between the enolate and the protonated form. Cyclization only occurs

(10) Montchamp, J. L.; Tian, F.; Hart, M. E.; Frost, J. W. *J. Org. Chem.* **1996**, *61*, 3897.
(11) Hatch, R. P.; Weinreb, S. M. *J. Org. Chem.* **1977**, *42*, 3960.

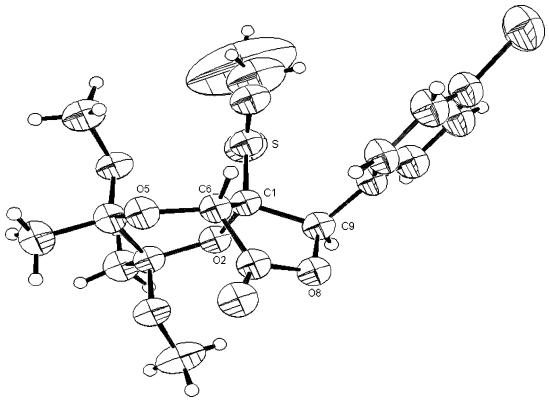


FIGURE 4. ORTEP plot (50% probability ellipsoids) of the molecular structure of *S*-ethyl (1*R*,3*R*,4*R*,6*R*,9*R*)-3,4-dimethoxy-3,4-dimethyl-7-oxo-9-(4-chlorophenyl)-2,5,8-trioxabicyclo[4.3.0]-nonane-1-thioate (**6**).

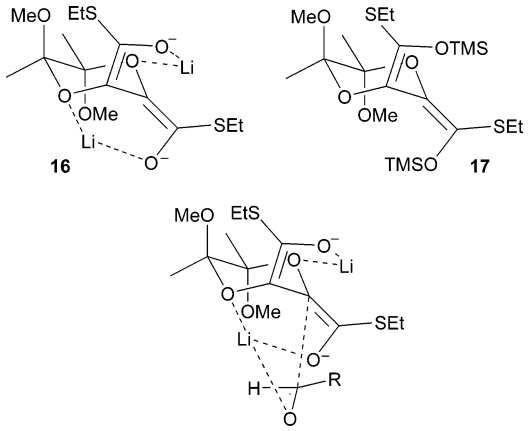
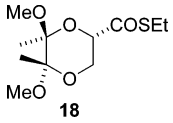


FIGURE 5. Possible transition state for the lactonization reaction.

when the cis lactone is formed. Where steric hindrance is strong, lactonization is slow or impossible and no aldol products are observed due to the facility of the reverse reaction. This was evident from studies with pivalaldehyde and ketones, where only small amounts or no lactonised aldol products were isolated and starting material recovered. 4-Nitrobenzaldehyde furnished a high yield of the unsaturated compound **14** and although we did not isolate an equivalent amount of alcohol we suspect that hydride is being expelled from the monoenolate forming the observed **14** and 4-nitrobenzyl alcohol. The carbonyl group of 4-nitrobenzaldehyde is a good hydride acceptor and considerably better than any of the other aldehydes in this respect. On the other hand, it should also be a good electrophile, reacting with the enolate to form a stabilized alkoxide, which perhaps does not cyclize easily and undergoes a reverse aldol. The result of these competing reactions is the oxidized product observed. Other redox mechanisms are possible but we feel they are less likely than the hydride transfer mode.

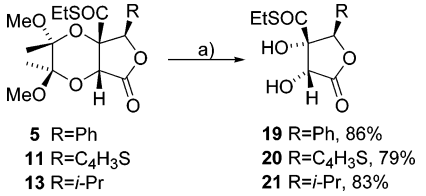
This behavior was not observed for the dioxane **18** (Figure 6), derived from glyceric acid, which underwent efficient aldol reactions with both aldehydes and ketones to afford hydroxyesters[12] and indicates the ease with which oxidation to the stable enedioate system **14** occurs.



18

FIGURE 6. Dioxane thioester derived from glyceric acid.

SCHEME 2[a]



5 R=Ph
11 R=C_4H_3S
13 R=*i*-Pr

19 R=Ph, 86%
20 R=C_4H_3S, 79%
21 R=*i*-Pr, 83%

[a] Reagents and conditions: (a) $BF_3{\cdot}OEt_2$, $HS(CH_2)_2SH$, CH_2Cl_2, 80 °C[3] or TFA/H_2O rt.

Thus a critical limitation to the use of this process for synthesis was encountered. Severe steric interactions reduce the amount of aldol product formed and the unreacted enolate is quenched at the workup to afford isomers of the starting material.The removal of the dioxane acetal[3] (Scheme 2) of the aldol products **5** and **13** was easily performed with ethanedithiol and $BF_3{\cdot}OEt_2$ to afford diols **19** and **21** in good yields. For lactone **11** the use of $BF_3{\cdot}OEt_2$ proved to be unsuccessful and a mixture of TFA/water was used instead, affording diol **20** in 79% yield.

Conclusions

The study of aldol reactions with use of the lithium enolates derived from thioester **1** has been carried out. Electrophilic quenching with a varied selection of aliphatic and aromatic aldehydes gave good chemical yields and high stereoselectivity was achieved. The absolute configurations of the obtained lactones were assigned as (1*R*,6*R*,9*R*) except for the thiophene derivative which has (1*S*,6*R*,9*S*). Steric hindrance when using large aldehydes causes a severe limitation to the scope of this reaction. A possible transition state is proposed. The γ-lactones obtained can, after hydrolysis of the dioxane acetal, be applied as intermediates in asymmetric organic synthesis.

Experimental Section

General Procedure for the Syntheses of Lactones. (A) Compounds 5−13. The synthesis of compounds **5**−**13** was carried out by following a previously reported procedure[3] with some modifications: To a solution of $(i\text{-Pr})_2NH$ (0.194 mL, 1.38 mmol) in THF (4.5 mL) at 0 °C was added *n*-BuLi (0.781 mL, 1.25 mmol) drop by drop. The reaction mixture was stirred at this temperature for 30 min, then cooled at −78 °C, and after 15 min a solution of **2** (0.200 g, 0.57 mmol) in THF (3.0 mL) was slowly added. Stirring at −78 °C was continued for a further 45 min and a solution of aldehyde (1.42 mmol) in THF (1.0 mL) was then added. The reaction mixture was stirred at −78 °C for 120 min, and then at 0 °C for 20−30 min. The reaction was quenched with saturated NH_4Cl aqueous solution and stirred for 20 min. The aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL), the combined organic phases were dried with $MgSO_4$, and the solvent was evaporated. Purification by

(12) (a) Ley, S. V.; Michael, P.; Trapella, C. *Org. Lett.* **2003**, *5*, 4553. (b) Wahnon, J. R. Unpublished results.

medium-pressure column chromatography (hexane/AcOEt, 95/5) afforded the corresponding lactones.

General Procedure for the Dioxane Acetal Removal. (B) Compounds 19 and 21. To a solution of the corresponding lactone (0.227 mmol) in CH_2Cl_2 was added ethanedithiol (0.568 mmol) followed by a slow addition of $BF_3{\cdot}OEt_2$ (0.250 mmol). The reaction mixture was stirred at 80 °C in a sealed tube for 120 min. Workup with saturated $NaHCO_3$ aqueous solution and extraction with AcOEt (3 × 20 mL) afforded a yellow crude product. Purification by preparative layer chromatography (hexane/AcOEt, 7/3) afforded the corresponding diols. (**C**) **Compound 20.** To the lactone **11** (0.075 mmol) was added a mixture of TFA/water (9/1, 1 mL) and the reaction mixture was stirred for 180 min. After solvent evaporation the crude product was purified by preparative layer chromatography (hexane/AcOEt, 6/4) affording diol **20**.

The following are selected characterization data for the aldol reaction products. A full account of products characterization can be found in the Supporting Information.

***S*-Ethyl (1*R*,3*R*,4*R*,6*R*,9*R*)-3,4-Dimethoxy-3,4-dimethyl-7-oxo-9-(4-chlorophenyl)-2,5,8-trioxabicyclo[4.3.0]nonane-1-thioate (6)**. Lactone **6** was obtained following general procedure A as a white solid, in 61% yield. Mp 118−119 °C; $[\alpha]^{20}_D$ +12.3 (*c* 1.56, $CHCl_3$); ^{1}H NMR δ 7.30 (2H, d, J = 8.4 Hz), 7.12 (2H,d, J = 8.6 Hz), 5.44 (1H, s), 4.95 (1H, s), 3.41 (3H, s), 3.07 (3H, s), 2.61 (2H, m), 1.48 (3H, s), 1.41 (3H, s), 1.07 (3H, t, J = 7.4 Hz); ^{13}C NMR δ 197.1, 171.2, 135.2, 131.8, 128.6, 127.3, 101.8, 99.3, 86.7, 84.6, 66.4, 48.5, 47.9, 23.1, 18.3, 18.0, 14.2; FT-IR 2968, 2946, 1807, 1681, 1107; MS *m/z* 431 ($M^{+\bullet}$ + H, 2.3), 399 (52.6), 262 (52), 168 (29.2), 117 (59.3), 116 (100), 101 (41.2), 74 (30.0). Anal. Calcd for $C_{19}H_{23}ClO_7S$: C 52.96; H 5.38; S 7.44. Found: C 53.47; H 5.19; S 7.26.

***S*-Diethyl (2*R*,3*R*)-2,3-Dimethoxy-2,3-dimethyl-1,4-dioxene-5,6-dithioate (14)**. Compound **14** was obtained following general procedure A as white crystals, in 88% yield. Mp 82−83 °C; $[\alpha]^{20}_D$ −295.5 (*c* 1.65, $CHCl_3$); ^{1}H NMR δ 3.39 (6H, s), 2.97 (4H, m), 1.55 (6H, s), 1.30 (6H, t, J = 7.4 Hz); ^{13}C NMR δ 186.7, 133.1, 99.3, 49.7, 23.2, 16.8, 14.2; FT-IR 2964, 2930, 1677, 1613, 1143; MS *m/z* 351 (M^+ + H, 100.0), 290 (9.1), 116 (30.0). Anal. Calcd for $C_{14}H_{22}O_6S_2$: C 47.98; H 6.33; S 18.30. Found: C 48.10; H 6.41; S 18.20.

(2*R*,3*R*,4*R*)- 3,4-Dihydroxy-5-oxo-2-phenyltetrahydrofuran-3-carbothioic Acid *S*-Ethyl Ester (19). Diol **19** was obtained following general procedure B as a colorless viscous liquid, in 86% yield. $[\alpha]^{20}_D$ +183.9 (*c* 0.31, $CHCl_3$); ^{1}H NMR δ 7.35 (3H, m), 7.18 (2H, m), 5.56 (1H, s), 5.17 (1H, s), 2.69 (2H, m), 1.04 (3H, t, J = 7.3 Hz); ^{13}C NMR δ 198.7, 174.0, 132.8, 129.3, 128.5, 125.9, 87.4, 85.5, 69.6, 23.3, 14.0; FT-IR 3311, 1788, 1672, 1112, 1000; MS *m/z* 283 ($M^{+\bullet}$ + H, 37.8); 221 (24.2), 176 (100), 148 (70.3), 107 (36.2).

(2*S*,3*S*,4*R*)-3,4-Dihydroxy-5-oxo-2-thiophen-2-yltetrahydrofuran-3-carbothioic Acid *S*-Ethyl Ester (20). Diol **20** was obtained following general procedure C as a white solid, in 79% yield after recrystalization with hexane/AcOEt. Mp 113−114 °C. $[\alpha]^{20}_D$ −86.4 (*c* 0.49, $CHCl_3$); ^{1}H NMR δ 7.45 (1H, dd, J = 5.0 Hz, J = 1.1 Hz), 7.14 (1H, d, J = 3.5 Hz), 7.05 (1H, dd, J = 5.0 Hz, J = 3.7 Hz), 5.98 (1H, s), 5.00 (1H, s), 3.73 (1H, s broad), 2.92 (2H, q, J = 7.4 Hz), 1.26 (3H, t, J = 7.4 Hz); ^{13}C NMR δ 200.8, 172.6, 131.9, 128.6, 128.4, 126.7, 85.4, 79.6, 73.8, 23.8, 14.0; FT-IR 3441, 1788, 1663, 1263, 1134; MS *m/z* 290 (M^+ + H, 82.2), 270 (14.8), 227 (21.9), 209 (100). Anal. Calcd for $C_{11}H_{12}O_5S_2$: C 45.82; H 4.19. Found: C 46.15; H 3.90.

Acknowledgment. We thank Fundação para a Ciência e Tecnologia for valuable financial support and for a grant to J.D.L. (PRAXIS XXI/BD/17006/98) and J.R.W. (SFRH/BD/7296/2002).

Supporting Information Available: General experimental details and characterization data for all compounds and a CIF file. This material is available free of charge via the Internet at http://pubs.acs.org.

JO049027H