Transacetalization Reaction of Acetals by Lactic Acid. Diastereoselective Synthesis of 2-Substituted-5-methyl-1,3-dioxolan-4-ones

Jean-Yves Ortholand, Nicolas Vicart,† and Alfred Greiner*

Rhône Poulenc Secteur Agro, Centre de Recherches de La Dargoire, BP 9163 F-69263 Lyon Cedex 09, France

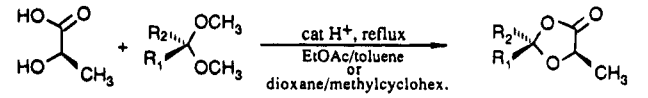
Received August 9, 1994

In connection with work on the synthesis of optically pure α-hydroxy-β-keto esters of biological interest, we developed a new procedure for highly diastereoselective preparation of 2,2-disubstituted 5-methyl-1,3-dioxolan-4-ones. Related dioxolanones have been widely used recently for several applications,[1] including the 1,3 chirality transfer principle.[2] Two general methods of formation[3] of these chiral building blocks were known at the beginning of our study, namely cyclization of a hydroxy acid or its bis(trimethylsilyl) derivative with a carbonyl compound. Both routes suffer from major drawbacks in the limited diastereoselectivity of cyclization as well as the poor reactivity of ketones. Furthermore, in most cases, the products are oils which are difficult to isolate in good yield and isomeric purity.[4]

Using the first of these methods with unusually hindered ketones and lactic acid led us to interesting new chiral building blocks,[5] but the reactivity of the starting carbonyl derivatives was still insufficient. We report herein results obtained by the acid-catalyzed transacetalization reaction of ketone dimethyl acetals with lactic acid. This new method permits preparation of crystalline dioxolanones in diastereomerically pure form allowing further access to enantiomerically pure α-hydroxy-β-keto esters.[6]

The stereoselective acid-catalyzed formation of dioxolanones from lactic acid and dimethyl acetals was unknown at the beginning of our study.[7] Others[3d] have used dimethyl acetals of carbonyl derivatives for dioxolanone formation starting from silylated α-hydroxy acids, but the yield and selectivity are identical to results obtained by using the same methodology on the parent ketones. In the case of direct acid-catalyzed cyclization, we thought that the poor reactivity of aromatic ketones might be improved by starting from the corresponding acetals. Furthermore, the easy azeotropic removal of methanol formed during the reaction would displace the equilibrium toward the cyclization products.

Scheme 1. Transacetalization Reaction of Dimethyl Acetals by Lactic Acid



(±) Lactic acid 1 **2a-e** (±) **3a-e**

The 2-substituted dioxolanones **3a–e** were obtained by transacetalization reaction of the dimethyl acetals **2a–e** with lactic acid (Scheme 1). These acetals were prepared by conventional techniques[8] from commercially available ketones[9] and were isolated in good yield after fractional distillation (See Experimental Section). Acetalization of α-tetralone using a very mild acid catalyst[10] gave us a 38:62 mixture of **2e** and the corresponding enol ether (elimination product). It was used without further purification. Lactic acid, available in 85% aqueous solution,[11] was used as a 1.5–2 M anhydrous solution in EtOAc or dioxane, prepared as described in the Experimental Section. After addition to the acetal solution (0.5–1 M in $PhCH_3$ or methylcyclohexane), the homogeneous mixture was heated at 90–100 °C to distill the volatiles (CH_3OH, excess orthoformate) in a Dean–Stark trap. When necessary, the acid catalyst was added directly to the hot reaction mixture (Table 1). After completion of the reaction (GC analysis), the hot solution was neutralized by TEA or DIEA to prevent any equilibration or secondary reaction and then cooled and worked up as described in the Experimental Section.

The results obtained by this new methodology concerning both cyclization selectivity and chemical yield are extremely interesting (Table 1). The dioxolanones are formed in moderate to high yield, even with the very hindered acetal **2a** or for **3b** and **3c** where the direct acid-catalyzed cyclization starting from acetophenone and acetonaphthone led to less than 5% conversion.[12] The stereoselectivity is in any case very high, allowing the formation of **3a,b** as diastereomerically pure products.[13]

† Present Address: Laboratoire de Chimie Organique 1. Université Claude Bernard Lyon 1, 43 Bd du 11 Novembre 1918, F-69622 Villeurbanne, France.

(1) Reddy, V. D. ; Franck, R. W. *J. Org. Chem.* **1993**, *58*, 6911. (b) Beckwith, A. L. J.; Chai, C. L. L. *Tetrahedron* **1993**, *49*, 7871. (c) Kneer, G.; Mattay, J. *Tetrahedron Lett.* **1992**, *33*, 8051. (d) Heckmann, B.; Mioskowski, C.; Yu, J.; Falck, J. R. *Tetrahedron Lett.* **1992**, *33*, 5201. (e) Roush, W. R.; Brown, B. B. *J. Org. Chem.* **1992**, *57*, 3380. (f) Moorlag, H.; de Vries, J. G.; Kaptein, B.; Schoemaker, H. E.; Kamphuis, J.; Kellogg, R. M. *Recl. Trav. Chim. Pays-Bas* **1992**, *111*, 129. (g) Mattay, J.; Mertes, J.; Maas, G. *Chem. Ber.* **1989**, *122*, 327. (h) Krysan, D. J.; Mackenzie, P. B. *J. Am. Chem. Soc.* **1988**, *110*, 6273. (i) Mashraqui, S. H.; Kellogg, R. M. *J. Org. Chem.* **1984**, *49*, 2513.

(2) Fráter, G.; Müller, U.; Günther, W. *Tetrahedron Lett.* **1981**, *22*, 4221. Seebach, D.; Imwinkelried, R.; Weber, T. In *Modern Synthetic Methods*; Scheffold, R., Ed.; Springer Verlag: Berlin Heidelberg, 1986; Vol 4, p 125 and references cited herein. For recent applications: Caldwell, C. G.; Rupprecht, K. M.; Bondy, S. S.; Davis, A. A. *J. Org. Chem.* **1990**, *55*, 2355. Boeckman, R. K., Jr.; Yoon, S. K.; Heckendorn, D. K. *J. Am. Chem. Soc.* **1991**, *113*, 9682. Kanda, Y.; Fukuyama, T. *J. Am. Chem. Soc.* **1993**, *115*, 8451.

(3) From α-hydroxy acids: (a) Farines, M.; Soulier, J. *Bull. Soc. Chim. Fr.* **1970**, 332. (b) Seebach, D.; Naef, R.; Calderari, G. *Tetrahedron* **1984**, *40*, 1313. From bis-silylated α-hydroxy acids: (c) Hoye, T. R.; Peterson, B. H.; Miller, J. D. *J. Org. Chem.* **1987**, *52*, 1351. (d) Pearson, W. H.; Chen, M.-C. *J. Org. Chem.* **1987**, *52*, 1353.

(4) For an example and a discussion, see ref 1e.

(5) Greiner, A.; Ortholand, J.-Y. *Tetrahedron Lett.* **1990**, *31*, 2135.

(6) Greiner, A.; Ortholand, J.-Y. *Tetrahedron Lett.* **1992**, *33*, 1897.

(7) This reaction was recently described independently for the temporary protection of lactic acid by 2,2-dimethoxypropane: Moorlag, H.; Kellogg, R. M.; Kloosterman, M.; Kaptein, B.; Kamphuis, J.; Schoemaker, H. E. *J. Org. Chem.* **1990**, *55*, 5878.

(8) Meškens, F. A. J. *Synthesis* **1981**, 501. We intended as well to prepare acetals from hindered 2,2-dimethyl-1-indanone and 2,2-dimethyl-α-tetralone (for the preparation of these ketones, see ref 9c) but none of the conditions we tried succeeded.

(9) The expensive 2,2-dimethylpropiophenone may be prepared according to litterature procedures. See: (a) Zadel, G.; Breitmaier, E. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1035. (b) Posner, G. H.; Whitten, C. H. *Organic Syntheses*; Wiley: New York, 1988; *Coll. Vol. VI*, p 248. (c) Lissel, M.; Neumann, B.; Schmidt, S. *Liebigs Ann. Chem.* **1987**, 263.

(10) Gasparrini, F.; Giovannoli, M.; Misiti, D. *Tetrahedron* **1984**, *40*, 1491.

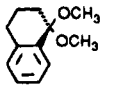
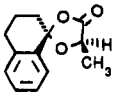
(11) Pure lactic acid is not stable and polymerizes upon standing. See: Van Ness, J. H. In *Encyclopedia of Chemical Technology*; John Wiley: New York, 1981; Vol. 13.

(12) Ortholand, J.-Y.; Greiner, A. *Bull. Soc. Chim. Fr.* **1993**, *130*, 133.

(13) For these dioxolanones, the chemical shifts of the *trans* isomers are known and their presence is not detected to the limit of sensitivity of 250 MHz ^1H NMR. In the case of **3a**, the characterization of the *trans* isomer led us to reevaluate the diastereoselectivity of formation, originally described as 95:5 (ref 5). For **3a** *trans* characterization and **3b** *trans* selective preparation, see ref 12.

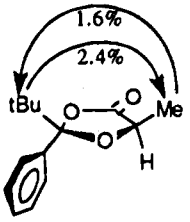
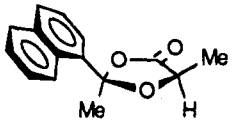
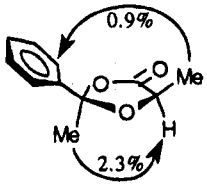
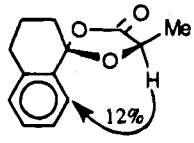
0022-3263/95/1960-1880$09.00/0

Table 1. Acid-Catalyzed Dimethyl Acetals Transacetalization by Lactic Acid

acetals 2 a-d R1	R2		catalyst	product	selectivity[a] cis:trans	yield (%)[b]
t-butyl	phenyl	2a	TfOH (PPTS)	3a	>98:2[c]	81[d] (50)[d]
naphthyl	methyl	2b	PPTS	3b	>98:2[c]	51[d]
phenyl	methyl	2c	none	3c	95:5	75
t-butyl	H	2d	TfOH (PPTS[e])	3d	96:4 (97:3)	82[f] (47-59)[f]
		2e	none (TsOH)		3e 95:5 (65:35)	43[a] (78)[a]

[a]Based on 250MHz ^{1}H NMR of the crude reaction mixture. [b]Isolated yield unless specified. [c]See ref 13. [d]Diastereomerically pure compound. [e]See ref 18. [f]Reaction time (hr): 1.75 (TfOH), 8 (PPTS).

Table 2. Relative Stereochemical Assignments by ^{1}H NOE and ^{1}H NMR Chemical Shifts

NOE	Chemical Shifts[a]	NOE	Chemical shifts[a]
	$\delta_{H\text{-}5}$ cis = 4.09 ($\Delta\delta_{trans}$ = + 0.51)[b] $\delta_{Me\text{-}5}$ cis = 1.50 ($\Delta\delta_{trans}$ = - 0.33)[b]		$\delta_{H\text{-}5}$ cis = 4.76 ($\Delta\delta_{trans}$ = - 0.48)[b] $\delta_{Me\text{-}5}$ cis = 1.37 ($\Delta\delta_{trans}$ = + 0.23)[b]
± 3a (isomerically pure)		± 3b (isomerically pure)	
	$\delta_{H\text{-}5}$ cis = 4.65 ($\Delta\delta_{trans}$ = - 0.56) $\delta_{Me\text{-}5}$ cis = 1.39 ($\Delta\delta_{trans}$ = + 0.05)		$\delta_{H\text{-}5}$ cis = 4.55 ($\Delta\delta_{trans}$ = + 0.20) $\delta_{Me\text{-}5}$ cis = 1.65 ($\Delta\delta_{trans}$ = - 0.06)
± 3c (major)		± 3e (minor)	

[a] Reported in ppm referenced to the TMS. [b]See ref 13.

The relative configuration of the products obtained was assigned by NOE experiments on major (**3a**, **3c**) or minor (**3e**) isomers (Table 2). In the case of **3b**, no NOE was observed and the relative configuration of the only isomer obtained was deduced to be as shown by chemical shift comparison of the two isomers with the related 5-methyl-2-naphthyl-1,3-dioxolan-4-one of known configuration.[12] These results show that the methyl group on the 5-position and the bulkiest substituent on the 2-position are in every case on the same side of the dioxolanone ring for the major isomer. We will refer to this configuration as *cis*.[14,15] This is in complete agreement with previous studies on dioxolanone formation[2,3a,b] by direct acid-catalyzed cyclization. Furthermore, valuable conformational informations can be deduced from ^{1}H NMR data: chemical shift differences observed on the 5-substituents between the two isomers ($\Delta\delta$, Table 2) may be explained by the shielding/deshielding effect of the 2-aromatic substituent. Thus for **3a**–**c**, this substituent is oriented as shown in order to shift upfield the 5-substituent in *cis* position. The opposite and locked conformation of the electron-rich ring in **3e** has a reverse deshielding effect on the 5-*cis* substituent and fully confirms this hypothesis. Complementary studies concerning the general conformation of dioxolanones have been published previously by other authors.[14,16]

Discussion

It is clear from results outlined in Table 1 that acidity of the reaction medium plays a dominant role in both yield and diastereoselectivity of dioxolanone formation.

(14) For a discussion on dioxolanone relative stereochemistry, see ref 3a, 12 and Salomaa, P.; Sallinen, K. *Acta Chem. Scand.* **1965**, *19*, 1054.

(15) This terminology matches the CIP rules for the nomenclature of asymmetric centers, except for **3a** where the major isomer is the *trans* according to these rules. See: Cahn, R.; Ingold, C.; Prelog, V. *Angew. Chem., Int. Ed. Engl.* **1966**, *5*, 385.

(16) Polonski, T. *Tetrahedron* **1983**, *39*, 3131.

Thus, we have shown that a dramatic increase in yield and rate of **3a** formation could be achieved going from mildly acidic PPTS[17] to TfOH without affecting the diastereoselectivity. Extending this important modification to our previous synthesis[18] of the well known 2-*tert*-butyl-5-methyl-1,3-dioxolan-4-one[2] (**3d**) starting from pivalaldehyde dimethyl acetal led us to the expected very short reaction time and improved yield without any change of isomer ratio (Table 1).

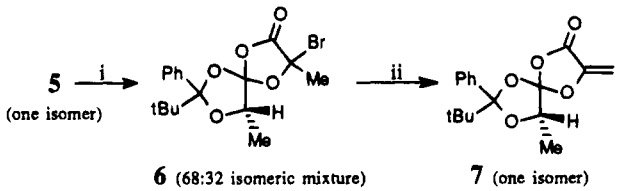
Further extension of this observation was somewhat disappointing as using TsOH for **3e** formation expectedly increased the reactivity of the acetal **2e**,[19] but at the expense of the stereoselectivity of the corresponding dioxolanone (**3e**, Table 1). These results may be explained considering the nature of the starting acetal. In the case of **2b** and **2e**, strongly acidic catalysis will favor fast methanol elimination leading to the corresponding conjugated enol ether. This intermediate may either cyclize with lactic acid to form the dioxolanone **3e** or decompose by possible polymerization (**3b**, TsOH catalysis). With the acetal **2a** and **2d**, such an elimination cannot take place under any acid catalysis. Equilibration toward the thermodynamic mixture under strong acid catalysis may be another explanation.[20]

For **3a** typical example, we identified possible secondary reactions in order to obtain reproducible yields and selectivity. Pivalophenone should be excluded from the reaction medium as we have shown previously[12] that it can slowly cyclize under these conditions with lactic acid to give **3a** with only 83% diastereoselectivity. The starting acetal is carefully distilled to remove nonacetalized ketone and is reacted under anhydrous conditions to avoid hydrolysis back to the carbonyl derivative. Furthermore, the acid catalyst is added to the reaction mixture at the optimized reaction temperature, since the acetal slowly decomposes in the presence of TfOH to regenerate the ketone. Finally, CH_3OH formed during the reaction is removed as soon as it is formed to drive the equilibrium and to prevent any methanolysis of the dioxolanone ring or any equilibration reactions.

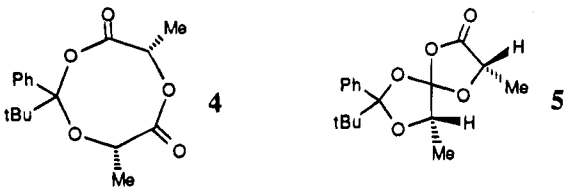
An interesting minor product of high molecular weight (as shown by GC) was formed under normal reaction conditions when equimolecular quantities of (*S*)-lactic acid and acetal **2a** were reacted together. This new diastereomerically pure compound was isolated by manual crystal separation of the crude product and further recrystallization. Although IR and mass spectral data agreed with the proposed structure **4**, the isomeric structure **5** was finally adopted[21] based on the ^{13}C NMR analysis since the spectra showed only one carbonyl resonance at 172.66 ppm and a resonance at 124.70 ppm, characteristic of an orthoester.

To unambiguously confirm this structure, the following degradation scheme was devised, based on chemistry developed independently in our laboratory[22] and by others[1g,23] (Scheme 2). Only monobromo derivative **6** was obtained as a 68:32 mixture of two isomers from **5** under NBS/AIBN conditions, *even with excess NBS*. The bromination is regiospecific and only takes place on the favored captodative[24] position of the molecule. Further treatment of this mixture by DBU in refluxing $PhCH_3$ led to a single vinylic compound **7**, easily identified by 250 MHz ^1H NMR.

Scheme 2.[a] Degradation Pathway of the Orthoester 5



[a] Key: (i) NBS, AIBN, CCl_4, reflux, 30 min (ii) DBU, toluene, reflux, 15 min.



The same synthetic sequence starting from **4** would have led to a dibrominated species giving after elimination a divinylic structure or two different vinylic species in the case of monobromination. All attempts to prepare **5** by **3a** acetalization by lactic acid failed and we believe that **5** is probably formed by the reaction of the starting acetal **2a** with lactic acid dimer[11] when the monomer is no longer available. This is confirmed by the fact that **5** formation was totally suppressed when starting from 1.7-fold optimized excess of lactic acid. The mechanism would be similar to the one described recently by others[25] for the formation of spiro orthoesters, involving an intermediate dioxolenium ion which is subsequently trapped intramolecularly by the carboxylate group of the lactyllactate to form the spiro system. The identification of **5**[21] as a single isomer again suggests a stereospecific transacetalization process.

We examined the results obtained by this transacetalization procedure in order to propose a rational explanation for the high selectivities observed. In each of the cases **3a**–**e**, the thermodynamically favored *cis*[15] isomer is preferentially formed, as expected from previous studies.[3a,14] Furthermore, the diastereoselectivity of cyclization is almost independent of the nature of the starting acetal and does not reflect the difference of energy between the two isomers. For these reasons, we believe that the transacetalization process is transition state controlled, leading to the kinetic product of the reaction. Starting from dimethyl acetals and using the experimental conditions described, the cyclization is a fast, nonreversible reaction. The cationic intermediate leading to the cyclized product could be sufficiently short-lived for the stereoselectivity to be explained by an S_N2 mechanism.[26] On the other hand, the usual acid-

(17) Miyashita, M.; Yoshokoshi, A.; Grieco, P. A. *J. Org. Chem.* **1977**, *42*, 3772.
(18) Chapel, N.; Greiner, A.; Ortholand, J.-Y. *Tetrahedron Lett.* **1991**, *32*, 1441.
(19) The same observation was made starting from the 4,7-dichloro-1-indanone dimethyl acetal: the expected dioxolanone was obtained under TsOH catalysis only (no reaction with PPTS), in a 50:50 diastereoisomeric mixture.
(20) We did show that *cis* **3a** is slowly equilibrated to a diastereomeric mixture upon extended reaction time under TfOH catalysis.
(21) All attempts to determine the relative stereochemistry of the acetalic and orthoester centers were unsuccessful.
(22) Ortholand, J.-Y. Ph. D. Thesis, Université Claude Bernard. Lyon, 1991.
(23) Zimmermann, J.; Seebach, D. *Helv. Chim. Acta* **1987**, *70*, 1104.
(24) Viehe, H. G.; Merényi, R.; Stella, L.; Janousek, Z. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 917.
(25) Balsamo, A.; Benvenuti, M.; Lapucci, A.; Macchia, B.; Nencetti, S.; Rossello, A. *J. Org. Chem.* **1991**, *56*, 2148.

catalyzed direct cyclization[2,3a,b,12] gives lower and more variable selectivity depending on the starting carbonyl compound. Diastereoselectivities are more closely related to the relative energy level of each isomer and the mixture obtained is probably closer to the thermodynamic product of the reaction. This hypothesis is confirmed by the fact that the water formed under these conditions is more slowly removed from the reaction media and may equilibrate or selectively hydrolyze[14] one of the two diastereoisomers.

In conclusion, we have developed a new transacetalization reaction starting from lactic acid and dimethyl acetals of carbonyl compounds. This highly stereoselective reaction allowed the preparation of new dioxolanones **3a–c** and **3e**. In the first two examples **3a,b**, the synthons were obtained as diastereomerically pure, crystalline materials allowing for easy isolation and purification. These building blocks represent an interesting complement to the existing and widely used dioxolanone **3d**, for which we developed a new and efficient synthesis using this methodology. Thus, **3a** has already been used for several applications in our laboratory, leading to enantiomerically pure α-hydroxy-β-keto esters[6] and α,β-dihydroxy esters[27] of biological relevance.[28]

Experimental Section

General. ^{1}H and ^{13}C NMR spectra were run at 250 MHz and 62.5 MHz respectively. Chemical shifts are reported in ppm referenced to the TMS (^{1}H) and to the center peak of $CDCl_3$ (^{13}C, 77.0 ppm), and J values are reported in hertz. All NMR spectra were run in $CDCl_3$ unless otherwise noted. Optical rotations were measured at the 589 nm sodium D line. Flash column chromatography was performed with Merck Kieselgel 60 (230–400 mesh ASTM) silica.

General Preparation of the Dimethyl Acetals. A solution of ketone (10 mmol), $(CH_3O)_3CH$ (13 mmol) and acid catalyst (0.5 mmol) in CH_3OH (100 mmol) was stirred at rt until conversion had stopped (GC). The mixture was quenched by addition of 30% aqueous NaOH solution (0.5 mL), evaporated to one-third of the initial volume, and then diluted with water. The aqueous layer was extracted with Et_2O, and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Dimethyl acetal purification was achieved through reduced pressure distillation.

General Method for Lactic Acid Drying. The exact quantity of water contained in commercially available aqueous solution of D-(−), L-(+) or *dl*-lactic acid was determined by Karl–Fischer titration. To a solution of 83.4% aqueous lactic acid (0.5 mol, 54 g) in 300 mL EtOAc or dioxane was added $(CH_3O)_3CH$ (0.5 mol, 54.6 mL). The resulting mixture was stirred overnight at rt under N_2 and used soon after to avoid polymerization.

Pivalophenone Dimethyl Acetal (2a). Pivalophenone (4.44 mol, 720.4 g) was converted using $(CH_3O)_3CH$ (8 mol, 849 g) and TsOH (5 g) in MeOH (2 L). Fractional distillation afforded **2a** (601 g, 69%) as a colorless oil: bp 115–120 °C (18 Torr); ^{1}H NMR 7.41–7.24 (m, 5 H), 3.33 (s, 6 H), 0.94 (s, 9 H); ^{13}C NMR 139.21, 129.18, 127.08, 126.78, 107.17, 51.80, 40.41, 26.94; MS *m/z* 193 (2, $[M - CH_3]^+$), 177 (9), 151 (100), 105 (20). Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 74.70; H, 9.72.

1-Acetonaphthone Dimethyl Acetal (2b). Acetonaphthone (17 g, 0.1 mol) was converted using $(CH_3O)_3CH$ (0.2 mol, 22 mL) and H_2SO_4 (0.05 mL) in MeOH (120 mL). Usual workup afforded **2b** (20.5 g, 95%) as a 95% pure colorless oil, which was used without further purification in order to avoid enol ether formation. **2b**: ^{1}H NMR 8.14–7.37 (m, 7 H), 3.23 (s, 6 H), 1.76 (s, 3 H); enol ether: ^{1}H NMR 8.14–7.37 (m, 7 H), 4.50 (d, J = 2.0, 1 H), 4.41 (d, J = 2.0, 1 H), 3.78 (s, 3 H).

Acetophenone Dimethyl Acetal (2c). Acetophenone (175 mL, 1.5 mol) was converted using $(CH_3O)_3CH$ (1.8 mol, 175 mL) and H_2SO_4 (0.1 mL) in MeOH (900 mL). Fractional distillation afforded **2c** (215 g, 86%) as a colorless oil: bp 78 °C (18 Torr); ^{1}H NMR 7.87–7.43 (m, 5 H), 3.26 (s, 6 H), 1.58 (s, 3 H). Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.25; H, 8.58.

Pivalaldehyde Dimethyl Acetal (2d). Pivalaldehyde (100 g, 1.16 mol) was converted using $(CH_3O)_3CH$ (0.93 mol, 101.6 mL) and H_2SO_4 (0.1 mL) in MeOH (500 mL). Fractional distillation afforded **2d** (105.6 g, 69%) as a colorless oil: bp 117–118 °C (760 Torr); ^{1}H NMR 3.78 (s, 1 H), 3.50 (s, 6 H), 0.90 (s, 9 H).

α-Tetralone Dimethyl Acetal (2e). α-Tetralone (13.3 mL, 0.1 mol) was converted using $(CH_3O)_3CH$ (0.2 mol, 22 mL) and PPTS (0.05 g) in MeOH (100 mL). Usual workup afforded a mixture (18.5 g, 94%) of **2e** and enol ether. The crude product was used without further purification in order to avoid complete formation of enol ether. **2e**: ^{1}H NMR 7.7–7.0 (m, 4 H), 3.20 (s, 6 H), 3.0–2.0 (m, 6 H); enol ether: ^{1}H NMR 7.7–7.0 (m, 4 H), 4.97 (t, J = 4.65, 1 H), 3.69 (s, 3 H), 3.0–2.0 (m, 6 H).

(2*R*,5*S*)-2-*tert*-Butyl-5-methyl-2-phenyl-1,3-dioxolan-4-one (3a). To a solution of 10.4 g (50 mmol) of dimethyl acetal **2a** in 100 mL of methylcyclohexane was added a solution of 8.4 g (80 mmol) of L-(+)-lactic acid in dioxane (50 mL). The mixture was heated to reflux in order to distill and collect the volatile solvants (CH_3OH, excess $(CH_3O)_3CH$) in a Dean–Stark trap. When the temperature had reached 90–95 °C, the reaction was initiated by adding 2 mL of a 5 mol % TfOH solution in dioxane. After 5–10 min during which CH_3OH was formed and removed, the hot reaction mixture was neutralized by 5 mL of DIEA and cooled to rt. To this solution was added 100 mL of water. The aqueous layer was extracted with 3 × 50 mL of Et_2O, and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by recrystallization (pentane) afforded **3a** (9.53 g, 81%) as colorless crystals: mp 101 °C; $[\alpha]^{21}_D$ +15.4 (*c* 2.04, $CHCl_3$); IR (Nujol) 1794 cm^{-1}; ^{1}H NMR 7.48–7.27 (m, 5 H), 4.09 (q, J = 6.0, 1 H), 1.50 (d, J = 6.0, 3 H), 1.01 (s, 9 H); ^{13}C NMR 173.99, 136.93, 128.77, 127.84, 127.53, 114.35, 70.47, 38.23, 24.43, 15.87; MS *m/z* 177 (38, $[M - C_4H_9]^+$), 105 (100). Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.77; H, 7.77.

(2*S*,5*S*)-2,5-Dimethyl-2-(1-naphthyl)-1,3-dioxolan-4-one (3b). To a solution of 10 g (46 mmol) of dimethyl acetal **2b** in 50 mL of $PhCH_3$ was added a solution of 7 g (65 mmol) of L-(+)-lactic acid in 50 mL of EtOAc. A catalytic amount (100 mg) of PPTS was added and the mixture was heated at 90 °C for 8 h while removing volatiles in a Dean–Stark trap. The solution was then neutralized by 3 mL of TEA and cooled to rt. To the resulting mixture was added 100 mL of saturated aqueous $NaHCO_3$ solution. The aqueous layer was extracted with 3 × 50 mL of Et_2O, and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by recrystallization (EtOAc) afforded **3b** (5.85 g, 52%) as colorless crystals: mp 129 °C; $[\alpha]^{22}_D$ +68 (*c* 2.01, $CHCl_3$); IR (Nujol) 1798 cm^{-1}; ^{1}H NMR 8.45 (d, J = 8.3, 1 H), 7.92–7.83 (m, 3 H), 7.61–7.44 (m, 3 H), 4.76 (q, J = 6.9, 1 H), 2.08 (s, 3 H), 1.37 (d, J = 6.9, 3 H); ^{13}C NMR 173.37, 137.10, 134.27, 130.03, 129.29, 128.83, 126.34, 125.71, 124.71, 122.87, 111.22, 70.62, 28.32, 17.17; MS *m/z* 242 (20, $[M^+]$), 227 (16), 155 (100), 127 (29). Anal. Calcd for $C_{15}H_{14}O_3$: C, 74.36; H, 5.82. Found: C, 74.02; H, 6.27.

(2*S*,5*S*)-2,5-Dimethyl-2-phenyl-1,3-dioxolan-4-one (3c). To a hot solution (90 °C) of 100 g (0.6 mol) of dimethyl acetal **2c** in 720 mL of $PhCH_3$ was added dropwise over 1 h a solution of 80 g (0.89 mol) of L-(+)-lactic acid in 400 mL of EtOAc. The resulting mixture was heated for an additional 1 h at 100 °C. The total volume of volatile solvants removed in the Dean–Stark trap during the reaction was *ca.* 300 mL. The solution was then neutralized by C_5H_5N (50 mL) and cooled to rt. To the resulting mixture was added 500 mL of saturated aqueous $NaHCO_3$ solution. The aqueous layer was extracted with 3 × 150 mL of Et_2O, and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by fractional distillation gave 84 g (75%) of a colorless oil (isomeric mixture: 95/5). Cis isomer **3c** (63 g; 75%) was further isolated by low temperature recrystallization (2:1 pentane/i-

(26) Amyes, T. L.; Jencks, W. P. *J. Am. Chem. Soc.* **1989**, *111*, 7900.
(27) Vicart, N.; Ortholand, J.-Y.; Emeric, G. Y.; Greiner, A. *Tetrahedron Lett.* **1994**, *35*, 3917.
(28) Dumas, R.; Job, D.; Ortholand, J.-Y.; Emeric, G. Y.; Greiner, A.; Douce, R. *Biochem. J.* **1992**, *288*, 865.

Pr_2O): bp 70 °C (0.2 Torr); $[\alpha]^{23}_D$ +69 (*c* 1.52, $CHCl_3$); IR (Nujol) 1799 cm^{-1}; ^1H NMR 7.55–7.36 (m, 5 H), 4.65 (q, *J* = 6.9, 1 H), 1.83 (s, 3 H), 1.39 (d, *J* = 6.9, 3 H); ^{13}C NMR 173.47, 141.11, 129.08, 128.36, 124.77, 110.23, 70.96, 27.65, 17.22; MS *m*/*z* 192 (8, $[M^+]$), 177 (48), 105 (100). Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.74; H, 6.29. Found: C, 68.41; H, 6.28.

(2*S*,5*S*)-2-*tert*-Butyl-5-methyl-1,3-dioxolan-4-one (3d). A mixture of 5.3 g (40 mmol) of dimethyl acetal **2d** and 4.46 g (50 mmol) of L-(+)-lactic acid in 40 mL of dioxane and 80 mL methylcyclohexane were heated to reflux while removing 18 mL of volatile material in a Dean–Stark trap (temp: 80–92 °C). A solution of 0.25 mL of TfOH in 2 mL of dioxane was then added dropwise to the reaction mixture. An additional 15 mL of volatile material was separated. After 1 h, an additional 0.25 equiv (1.48 g, 17 mmol) of lactic acid was added to convert the acetal (GC control). The hot reaction mixture was then neutralized by 5 mL of DIEA and cooled to rt. To this solution was added 100 mL of saturated aqueous $NaHCO_3$ solution. The aqueous layer was extracted with 3 × 50 mL of Et_2O, and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by bulb-to-bulb distillation afforded **3d** (5.2 g, 82%) as a colorless oil (isomeric mixture: 96/4): bp 85 °C (30 Torr); $[\alpha]^{27}_D$ +42 (*c* 1.8, $CHCl_3$) (lit.[2] $[\alpha]^{20}_D$ +44 (*c* 1.83, $CHCl_3$)); ^1H NMR 5.12 (s, 1.H), 4.38 (q, *J* = 5.3, 1 H), 1.50 (d, *J* = 5.3, 3 H), 0.99 (s, 9 H). Other spectroscopic data were in accordance with those reported previously.[2]

3,4-Dihydro-1(2*H*)-naphthalenespiro-2-(5′-methyl-1′-dioxolan-4′-one) (3e). To a hot solution (90 °C) of 6.75 g (40 mmol) of **2e** in 70 mL of $PhCH_3$ was added dropwise over 1 h a solution of 4.05 g (45 mmol) of *dl*-lactic acid in 20 mL of EtOAc. The resulting mixture was heated for an additional 1 h at 95 °C. The total volume of volatile solvents removed in the Dean–Stark trap during the reaction was *ca.* 12 mL. The solution was then neutralized by 5 mL of C_5H_5N and cooled to rt. To the resulting mixture was added 70 mL of saturated aqueous $NaHCO_3$ solution. The aqueous layer was extracted with 3 × 70 mL of Et_2O, and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo to afford crude **3e** (6.62 g, 43%) as a 95:5 mixture of isomers: ^1H NMR **major isomer** 7.40–7.15 (m, 4 H), 4.55 (q, *J* = 7.0, 1 H), 2.87 (t, *J* = 6.5, 2 H), 2.3–2.0 (m, 4 H), 1.65 (d, *J* = 7.0, 3 H); **minor isomer** 7.40–7.15 (m, 4 H), 4.75 (q, *J* = 7.0, 1 H), 2.87 (t, *J* = 6.5, 2 H), 2.3–2.0 (m, 4 H); 1.59 (d, *J* = 7.0, 3 H).

2-*tert*-Butyl-4,8-dimethyl-2-phenyl-1,3,6,9-tetraoxaspiro-[4.4]nonan-7-one (5): minor compound isolated as single isomer during optimization studies of **3a** synthesis. Purification by recrystallization (pentane). mp 108 °C; IR (Nujol) 1811 cm^{-1}; ^1H NMR 7.44–7.41 (m, 2 H), 7.33–7.31 (m, 3 H), 4.67 (q, *J* = 6.75, 1 H), 3.87 (q, *J* = 6.25, 1 H), 1.40 (d, *J* = 6.75, 3 H), 1.31 (d, *J* = 6.25, 3 H), 0.95 (s, 9 H); ^{13}C NMR 172.66, 138.43, 128.01, 127.79, 127.10, 124.70, 115.04, 76.04, 70.16, 38.05, 24.67, 16.63, 12.81; MS *m*/*z* 291(<1, $[M - CH_3]^+$), 249 (43, $[M - C_4H_9]^+$), 177 (48), 105 (100).

8-Bromo-2-*tert*-butyl-4,8-dimethyl-2-phenyl-1,3,6,9-tetraoxaspiro[4.4]nonan-7-one (6). To a solution of **5** (1 g, 3.2 mmol) in 10 mL of CCl_4 was added 0.6 g (3.4 mmol) of NBS and 10 mg of AIBN. The resulting mixture was heated at reflux for 30 min, then cooled to rt and diluted with 20 mL of water. The aqueous layer was extracted with 3 × 10 mL of Et_2O, and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo to afford crude **6** (1.08 g, 85%) as a 68:32 mixture of isomers: ^1H NMR **major isomer** 7.41–7.24 (m, 5 H), 3.84 (q, *J* = 6.4, 1 H), 2.00 (s, 3 H), 1.25 (d, *J* = 6.4, 3 H), 0.93 (s, 9 H); **minor isomer** 7.41–7.24 (m, 5 H), 3.95 (q, *J* = 6.0, 1 H), 2.15 (s, 3 H), 1.45 (d, *J* = 6.0, 3 H), 0.91 (s, 9 H).

2-*tert*-Butyl-4-methyl-8-methylene-2-methyl-1,3,6,9-tetraoxaspiro[4.4]nonan-7-one (7). To a crude solution of **6** (0.9 g, 2.9 mmol) in 15 mL of $PhCH_3$ was added 0.6 mL (4 mmol) of DBU. The resulting mixture was refluxed for 15 min and then cooled to rt and diluted with 10 mL of water. The aqueous layer was extracted with 3 × 5 mL of Et_2O, and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo to afford 0.3 g (40%) of crude **7** as a single isomer: ^1H NMR 7.50–7.09 (m, 5 H), 5.10 (d, *J* = 2.4, 1 H), 4.87 (d, *J* = 2.4, 1 H), 4.08(q, *J* = 6.0,1 H), 1.50 (d, *J* = 6.0, 3 H), 1.00 (s, 9 H).

Acknowledgment. We are grateful to Pr. Jacques Goré (Université Cl.Bernard Lyon I) for helpful suggestions and to the Ministère de la Recherche et de l'Espace for financial support. We thank the staff of the Analytical Department (Rhône-Poulenc Agro) for spectral analysis.

Supplementary Material Available: Copies of ^1H NMR spectra of **2b**, **2e**, and **5** (3 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO941384C