Optically Pure Dihydroxy γ-Alkylated γ-Butyrolactones Starting from L-Tartaric Acid: Application to Formal and Total Syntheses of Natural Products

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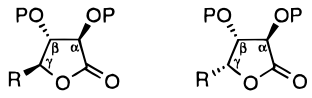
A general and efficient preparation of epimeric optically pure γ-butyrolactones **2** and **3** is described starting from L-tartaric acid (**1**). These lactones are well-known to be important building blocks in the syntheses of natural products. L-Tartaric acid (**1**) was transformed into carbonylated chirons (ketones **4** and aldehyde **5**). These chirons, when submitted to highly stereoselective reactions (reduction or organometallic addition), led to epimeric dihydroxy γ-butyrolactones **2** and **3** after lactonization and deprotection steps. The resulting optically pure lactones are precursors of biological compounds and have allowed a total synthesis of L-biopterin and formal syntheses of quercus lactone, dodecanolactone, avenaciolide, and tetrahydrocerulenin.

Introduction

Optically pure γ-butyrolactones have often played a key role as building blocks in the syntheses of many types of natural products including antibiotics, pheromones, and antifungal and flavor components.[1]

Consequently, many methods dealing with the syntheses of chiral substituted γ-butyrolactones have been published during the last decade. Regarding γ-alkylated γ-butyrolactones, the syntheses rely upon using starting material from the chiral pool such as glutamic acid,[2] levoglucosenone,[3] ribonolactone,[4] glucose,[5] xylose,[6] or tartaric acid,[7] while other syntheses have taken advantage of chiral sulfoxides[8] or propargylic alcohols.[9] Several resolution procedures have been described,[10] as well as biochemical accesses using enzymatic hydrolyses[11] or reductions.[12] We have been recently interested in the stereoselective synthesis of the following γ-alkylated γ-butyrolactones as intermediates in natural product syntheses (Chart 1).

Chart 1



P : protective group
R : alkyl group

Indeed, many natural products possess a γ-lactonic moiety—notably, avenaciolide,[11d] γ-caprolactone,[9a] γ-dodecanolactone,[9a] quercus lactone,[3] and blastmycinone[13] —or are synthesized from a γ-butyrolactone as are chalcogran,[14] sulcatols,[2a] and cerulenins[9b] (Table 1).

The literature results clearly point out that the controlled construction of the stereogenic center at the γ carbon is troublesome and that the introduction of the required alkyl group lacks flexibility.

On the other hand, L-tartaric acid (**1**) is a inexpensive natural product that possesses two asymmetric carbons. Thus, a highly stereoselective reaction could take advantage of those two centers to induce asymmetry in the third. Furthermore, a stereodivergent strategy based on L-tartaric acid (**1**) could give access to two types of γ-alkylated γ-butyrolactones **2** and **3** that are epimers at the C4 level (Scheme 1) and that are pivotal chirons for the stereospecific syntheses of some natural compounds. We wish to present here a strategy that takes advantage of the two points presented above. Our approach puts forth the easy transformation of L-tartaric acid (**1**) either to ketoesters **4** or to aldoester **5** which are themselves convenient precursors of epimeric lactones **2** and **3**.

[⊗] Abstract published in *Advance ACS Abstracts,* May 15, 1997.

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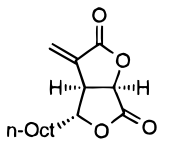
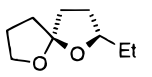
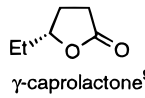
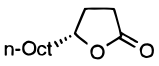
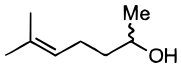
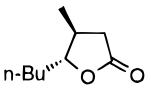
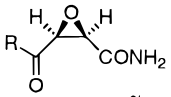
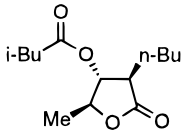
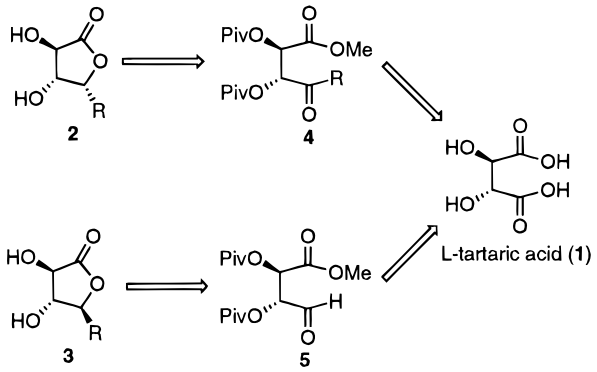
Table 1

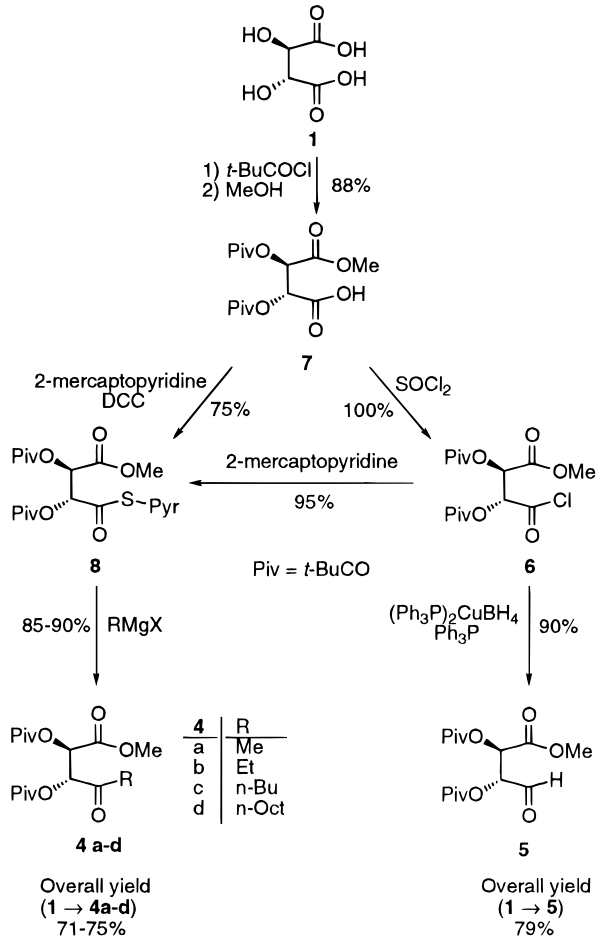
Natural compounds with a lactone moiety	Natural compounds prepared from γ-butyrolactones
 avenaciolide[11d]	 chalcogran[14]
 γ-caprolactone[9a]	
 γ-dodecanolactone[9a]	 sulcatols[2a]
 quercus lactone[3]	
	 cerulenins[9b]
 blastmycinone[13]	

Scheme 1



Synthesis of Carbonylated Chirons: Ketones 4 and Aldehyde 5. The general method for the preparation of these chirons is presented in Scheme 2. The hydroxyl functions of L-tartaric acid (**1**) were protected before undergoing further transformation: pivaloyl protecting groups were preferentially chosen instead of acetyl groups, the latter having provided unsatisfactory results.[15] Acid choride **6**, which can be prepared following a well-known literature procedure from L-tartaric acid (**1**),[16] is the common precursor of ketones **4** and aldehyde **5**.

Scheme 2



Preparation of Ketones 4. Conversion of L-tartaric acid (**1**) into ketones **4** required the preliminary synthesis of thioester **8**, which was achieved *via* either the acid choride **6**[17] or the acid **7**[18] (Scheme 2). An incomplete reaction and a partial hydrolysis of **8** during purification by chromatography on silica gel explained the decreased yield (75%) obtained by direct conversion of **7** to **8**. Consequently, synthesis of thioester **8** was more efficient using Mukaiyama's procedure[17] (95% yield from acid chloride **6**). Thioester **8** was submitted to a Grignard reaction, which introduced the alkyl residues R (Me, Et, *n*-Bu, *n*-Oct) for the preparation of the desired ketones **4a**−**d** (Scheme 2, Table 2).

Table 2 summarizes the results.

The addition of Grignard reagents occured exclusively on the thioester function and not on the ester moiety. Strict control of the reaction conditions avoided the formation of the undesirable dialkylated lactones **9**,[19] which were obtained as byproducts when more drastic conditions were employed (higher temperature—Table 2, entries 1, 4, and 6—or longer reaction time—Table 2, entries 2 and 7). An incomplete reaction was observed under more dilute conditions (Table 2, entries 9, 11). Ketones **4a**−**c** were obtained in 85−90% yield at −15 °C

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Table 2. Synthesis of Ketones 4a−d from Thioesters 8

entry	RMgX[a]	T (°C)	t (min)	ketone 4: yield[b] (%)	dialkylated lactone 9:[c] yield[b] (%)
1	3 M MeMgBr	−5	30	**4a**: 60	**9a**: 20
2		−15	60	**4a**: 68	**9a**: 12
3		−15	45	**4a**: 90	**9a**: 5
4	1 M EtMgBr	−5	30	**4b**: 70	**9b**: 6
5		−15	45	**4b**: 90	**9b**[d]
6	2 M *n*-BuMgCl	−5	30	**4c**: 87	**9c**: 3
7		−15	75	**4c**: 75	**9c**: 10
8		−15	45	**4c**: 90	**9c**[d]
9[e]		−15	45	**4c**: 60[e]	**9c**[d]
10	2 M *n*-OctMgCl	−15	75	no reaction	
11[e]		−5	75	**4d**: 50[e]	**9d**[d]
12		−5	75	**4d**: 85	**9d**[d]

[a] 1.1 equiv. [b] After chromatography. [c] See ref 19. [d] **9** is not detected. [e] Diluted medium (0.1 M in THF instead of 1 M in THF for other entries). Under these conditions, *ca.* 35% of the starting material **8** was retrieved after the experiment.

for 45 min (Table 2, entries 3, 5, and 8), whereas **4d** was obtained in 85% yield at −5 °C for 75 min (Table 2, entry 12).

Preparation of Aldehyde 5. This compound was prepared by reaction of acid chloride **6** with bistriphenylphosphine copper borohydride $(Ph_3P)_2CuBH_4$ under mild conditions[20] (Scheme 2). Two equiv of triphenylphosphine was added, one to bind to the copper byproduct and the other to trap liberated BH_3 (eq 1).

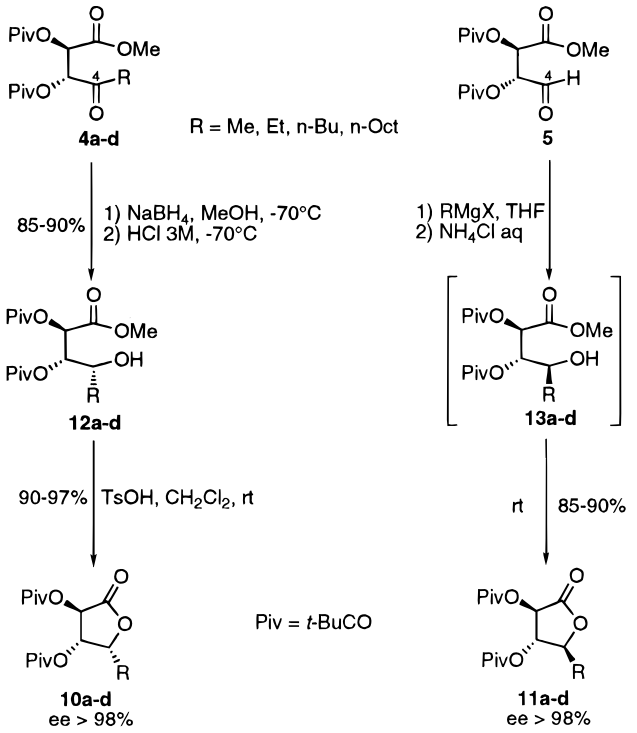
$$(Ph_3P)_2CuBH_4 + RCOCl \xrightarrow[rt]{2Ph_3P,\ acetone} (Ph_3P)_3CuCl + RCHO + Ph_3PBH_3 \quad (1)$$

The excess of Ph_3P was removed by stirring a chloroform solution of the crude product with cuprous chloride and then subjecting the resulting aldehyde **5** to purification by flash chromatography on silica gel. The complex $(Ph_3P)_3CuCl$ may be recycled to $(Ph_3P)_2CuBH_4$ in quantitative yield.[21] It is noteworthy that the reagent is unreactive toward all common functional groups with the exception of acid halides and iminium salts.[20d] Moreover, the reagent, which is inert to both oxygen and water, has an indefinite shelf life.

Finally, aldehyde **5** was obtained without epimerization in very good yield after purification (Scheme 2). Thus, L-tartaric acid (**1**) has allowed the preparation of two types of carbonylated chirons: the ketones **4** and the aldehyde **5**. They were obtained in very good yields on a multigram scale (Scheme 2).

Synthesis of γ-Alkylated γ-Butyrolactones 10 and 11. Development of highly stereoselective reactions was accomplished by reduction of ketones **4** and by addition of Grignard reagents to aldehyde **5**. A preferential attack occured on the *Si* face of carbonyl groups (ketone, aldehyde) (Scheme 3). Reduction of ketones **4** led to alcohols **12**, which after a lactonization step, yielded lactones **10**.

Scheme 3



On the other hand, Grignard reactions on aldehyde **5** led directly to lactones **11** (epimers of **10**) without isolation of intermediate alcohols **13**. Both series of lactones were obtained in optically pure form.

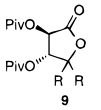
Reduction of Ketones 4. Preliminary experiments have been run mainly on the ketone **4c** (R = *n*-Bu) (Table 3, entries 1−7) and on ketone **4a** (R = Me) (Table 3, entry 8).

Lactone **10c** (major product) was directly obtained with $Zn(BH_4)_2$ when used either in THF (Table 3, entry 1) or in a mixture of solvents (Table 3, entry 2) as well as with $NaBH_4$ in THF (Table 3, entry 3). In these cases, yields and de were poor.

As is usually observed, the reactivity of $NaBH_4$ is dependent on the solvent. In EtOH, ketone **4c** was not reduced at all at −15 °C (Table 3, entry 4) but was totally reduced into diol **i**[22] at 0 °C (Table 3, entry 5). On the other hand, excellent results were obtained when $NaBH_4$ was used in MeOH, followed by acidic hydrolysis (Table 3, entry 6). In this case, alcohol **12c** was isolated in both very good yield and high de. The spontaneous lactonization, which occurred in THF and Et_2O (Table 3, entries 1−3), was not observed because of the protonation of the intermediate alkoxide by MeOH.

In a complementary study, we tried to modify the stereoselectivity at the C4 level by using either cerium chloride as an additive[23] with $NaBH_4$ (Table 3, entry 7) or by using another reducing agent (Table 3, entry 8). However, the expected inversion was not observed. In

(19) The byproduct **9** resulted from a partial dialkylation of the thioester **8** in some experiments.



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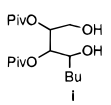
(22) Formation of diol **i**, in two cases, during the reduction with $NaBH_4$: (a) $NaBH_4$, EtOH, 0 °C (Table 3, entry 5); (b) $NaBH_4$, MeOH, −70 °C followed by hydrolysis with H_2O.



i

Table 3. Reduction of Ketones 4. Preliminary Experiments

entry	starting material	reducing agent (equiv)	solvent	*T*, °C (time, h)	workup conditions (*T*, °C)	major product: yield[a] (%) (de (%))
1	**4c**	$Zn(BH_4)_2$ (2.5)	THF	-10 (1) and rt (2)	HCl 3M (0)	**10c**: 60 (70)
2			Et_2O/THF 1/1	−10 (1) and rt (2)	HCl 3M (0)	**10c**: 50 (60)
3	**4c**	$NaBH_4$ (0.8)	THF	−70 (1)	H_2O (−70)	**10c**: 47 (40)
4		(1.5)	EtOH	−15 (1)	H_2O (−15)	no reaction
5		(2)	EtOH	0 (1)	H_2O (0)	**diol i**:[b] 50
6		(1.1)	MeOH	−70 (45 min)	HCl 3 M (−70)	**12c**: 85 (>98)
7	**4c**	$NaBH_4$ (1) $CeCl_3-7H_2O$ (1)	MeOH	−70 (1)	H_2O (−70)	**12c**: 60 (>98)
8	**4a**	$NaBH(OAc)_3$ (2)	CH_2Cl_2	rt (4)	H_2O	**12a**: 60 (>98)

[a] Chromatographed product. [b] See ref 22.

Table 4. Reduction of Ketones 4a−d with $NaBH_4$. Optimized Conditions[a]

R	alcohol **12**	*t*	yield[b] (%)	ee[c] (%)
Me	**12a**	3 h 30 min	80[d]	>98
Et	**12b**	1 h	85	>98
n-Bu	**12c**	45 min	85	>98
n-Oct	**12d**	75 min	90	>98

[a] 1.1 equiv of $NaBH_4$, MeOH, −70 °C. [b] After chromatography. [c] As checked by ^1H NMR. [d] Accompanied by 10% of lactone **10a**.

Table 5. Lactonization of Alcohol 12d. Preliminary Experiments

entry	time (h)	TsOH (equiv)	products (yield (%))
1	24	1	**10d** (60), **14d**[a] (20)
2	4	0.5	**10d** (70), **12d** (30)
3	4	1	**10d** (90)[b]
4	4	2	**10d** (80), **14d**[a] (20)

[a] See ref 25. [b] After chromatography, ee >98%.

Table 6. Lactonization of Alcohols 12a−d. Optimized Conditions[a]

R	lactone **10**	yield[b] (%)	ee[c] (%)
Me	**10a**	97	>98
Et	**10b**	95	>98
n-Bu	**10c**	95	>98
n-Oct	**10d**	90	>98

[a] 1 equiv of TsOH, 4 h, rt. [b] After chromatography. [c] As checked by ^1H NMR, showing no signals of epimeric lactones **11**.

Table 7. Grignard Reaction on Aldehyde 5

RMgX (1.5 equiv)	*T* (°C)	*t* (h)	lactone **11**: yield[a] (%)
MeMgBr 3 M in Et_2O	−70 and rt	12 2	**11a**: 88
EtMgBr 1 M in THF	−50 and rt	3 2	**11b**: 85
n-BuMgCl 2 M in THF	−25 and rt	2 2	**11c**: 90
n-OctMgCl 2 M in THF	−25 and rt	1 3	**11d**: 90

[a] After chromatography, ee > 98%, as checked by ^1H NMR (showing no signals of epimeric lactones **10**).

all cases, the same alcohol was obtained with excellent de, suggesting a very strong substrate control for the asymmetric induction.

The best conditions ($NaBH_4$, MeOH, −70 °C, followed by acidic hydrolysis) were extended to the other ketones **4**, giving satisfactory results in all cases (Scheme 3, Table 4).

Alcohols **12** were obtained with high stereoselectivity and good yields using the procedure previously described. In contrast to the literature,[24] we observed that the reduction by $Zn(BH_4)_2$ was less stereoselective than by $NaBH_4$ when carried out on our chirons.

Lactonization Step of Alcohols 12. TsOH in CH_2Cl_2 was used for lactonization (Scheme 3). The determination of optimized conditions was carried out using the alcohol **12d** (R = *n*-Oct) (Scheme 3, Table 5).

Extended reaction times or excess TsOH resulted in the formation of lactone **14d** (C2 epimer of lactone **10d**, Table 5). Moreover, incomplete conversion was observed when less than 1 equiv of TsOH was used (Table 5, entry 2). Best conditions were obtained in the presence of 1 equiv of TsOH (Table 5, entry 3). This method was applied to the cyclization of other alcohols **12** (Table 6).

Using these conditions, the synthesis of four optically pure γ-alkylated γ-butyrolactones **10** was achieved (Scheme 3). No epimeric lactones **11** or **14** were detected. The relative configuration of lactones **10** was determined by high-field NMR analysis (NOEDS).[26]

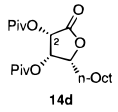
Grignard Reaction on Aldehyde 5. After the search for the best reaction conditions, we observed that addition of Grignard reagents led to lactones **11** with high stereoselectivity (ee > 98%) without isolation of the intermediate alcohols **13** (Scheme 3, Table 7). The addition step was performed at low temperature, and the lactonization occurred during warming to rt, yielding lactones **11** in both good yields (85−90%) and high ee (>98%) (Table 7).

These lactones are the C4 epimers[27] of those obtained by reduction of ketones **4** (Scheme 3). This approach

(23) (a) Gemal, A. L.; Luche, J. L. *J. Am. Chem. Soc.* **1981**, *103*, 5454. (b) Krief, A.; Surleraux, D.; Frauenrath, H. *Tetrahedron Lett.* **1988**, *29*, 6157. (c) Krief, A.; Surleraux, D. *Synlett* **1991**, 273.

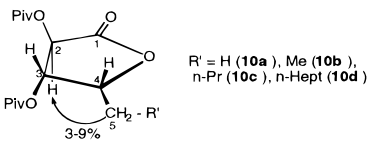
(24) (a) Nakata, T.; Oishi, T. *Tetrahedron Lett.* **1980**, *21*, 1641. (b) Nakata, T.; Tanaka, T.; Oishi, T. *Tetrahedron Lett.* **1981**, *22*, 4723. (c) Iida, H.; Yamazaki, N.; Kibayashi, C. *J. Org. Chem.* **1986**, *51*, 3769.

(25) Lactone **14d**, epimer in C2 of the desired lactone **10d**, was observed under the following conditions—long duration time or excess of TsOH—during the lactonization step (Table 5, entries 1−4). Irradiation of the proton H4 led to a selective Overhauser effect on H2 (4%).

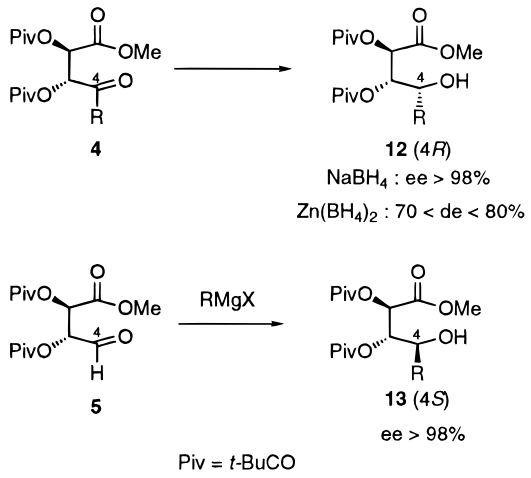


14d

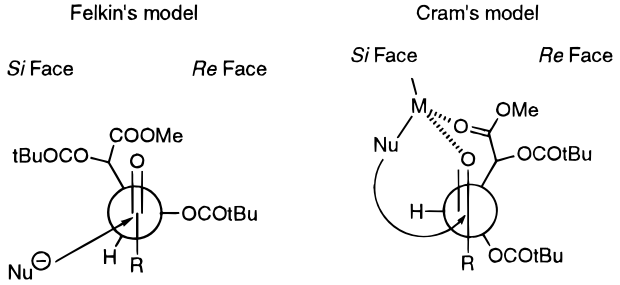
(26) Fernandez, A. M.; Jacob, M.; Gralak, J.; Al-Bayati, Y.; Plé, G.; Duhamel, L. *Synlett* **1995**, 431. Irradiation of the protons on C5 has led to the unambigous observation of a selective Overhauser effect on H2 from 3 to 9%.



Scheme 4



Scheme 5



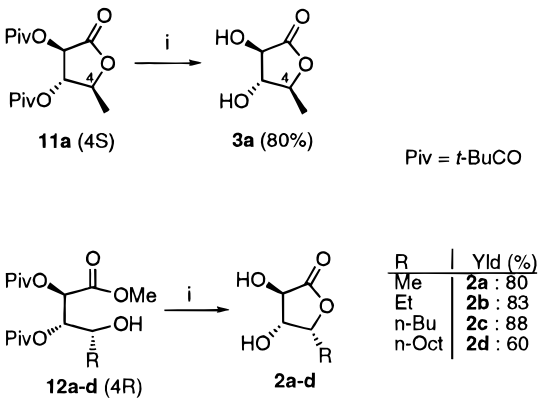
constitutes an efficient stereodivergent method to obtain optically pure γ-butyrolactones (Scheme 3), since the two complementary routes (*via* ketones **4** or *via* aldehyde **5**) yield, in optically pure form, eight epimeric protected lactones **10** and **11** starting from a single precursor, L-tartaric acid (**1**).

Discussion for the Observed Selectivity. Results for the addition and reduction steps are summarized in Scheme 4.

The same induction sense and level of selectivity are observed in reactions of ketones **4** with $NaBH_4$ and of aldehyde **5** with RMgX. This suggests that the transition state could be similar. Moreover, it is well-known that the contribution of the chelated transition state (Cram's model,[28] Scheme 5) involving the sodium cation is not favored, especially in alcohols as solvents.[29] For these two reasons, Felkin's model[30] is the more appropriate in both cases ($NaBH_4$ and RMgX) (Scheme 5). In this model, the more polar group is located at the side opposite to the entry of the nucleophile leading to the observed selectivity in which the attack occurs at the *Si* face.

Synthesis of Dihydroxy Lactones 2 and 3: Deprotection Step. In the (4*R*) series, this step has been run either from alcohols **12** or from lactone **10a** (90% yield) in acidic conditions. In both cases, the lactone **2** was directly obtained. In the (4*S*) series, only the lactone **11a** has been deprotected (Scheme 6).

Scheme 6[a]



[a] Key: (i) HCl 3 M/dioxane 2/1 reflux, 18 h (except R = *n*-Oct, *t* = 48 h)

Lactones **2a**−**c** and **3a** were obtained following the same procedure (refluxing in dioxane with HCl 3 M for 18 h) (Scheme 6). For the lactone **2d** (R = *n*-Oct), the deprotection was more fastidious. The corresponding protected lactone **10d** remained present even when the reaction time was increased. This slower deprotection rate may be due to the steric hindrance of the octyl group. Optical rotations of dihydroxy lactones **2d** and **3a** were in total agreement with literature values[7c,31] (see the Experimental Section). Thus, both lactonization and deprotection were carried out without epimerization.

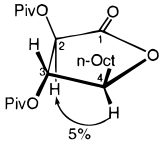
In this part of the work, five of the eight protected lactones **10** and **11** have been deprotected, and some of them are precursors of natural products. The following part describes the synthetic utility of these compounds.

Synthetic Applications of Optically Pure Lactones 2 and 3. Formal Syntheses of Natural Products Starting from 2c,d. Quercus lactone,[32] dodecanolactone,[33] avenaciolide,[34] and tetrahydrocerulenin[35] have been prepared from the corresponding butenolides (Scheme 7). As the synthesis of these butenolides has been carried out from dihydroxy lactones **2c** and **2d**, we have realized the formal syntheses of all these products with overall yields comparing favorably well with literature syntheses (Scheme 7).

Obviously, with the method described here, all these products can be synthesized in optically pure form. Since D-tartaric acid is also a cheap commercially available material, both enantiomeric forms can be prepared with this method.

Total Synthesis of L-Biopterin Starting from 3a. Through its tetrahydro form, L-biopterin functions as an essential enzyme cofactor in the metabolism of amino acids. For example, it plays a well-documented role for the conversion of phenylalanine to tyrosine,[37] tyrosine to

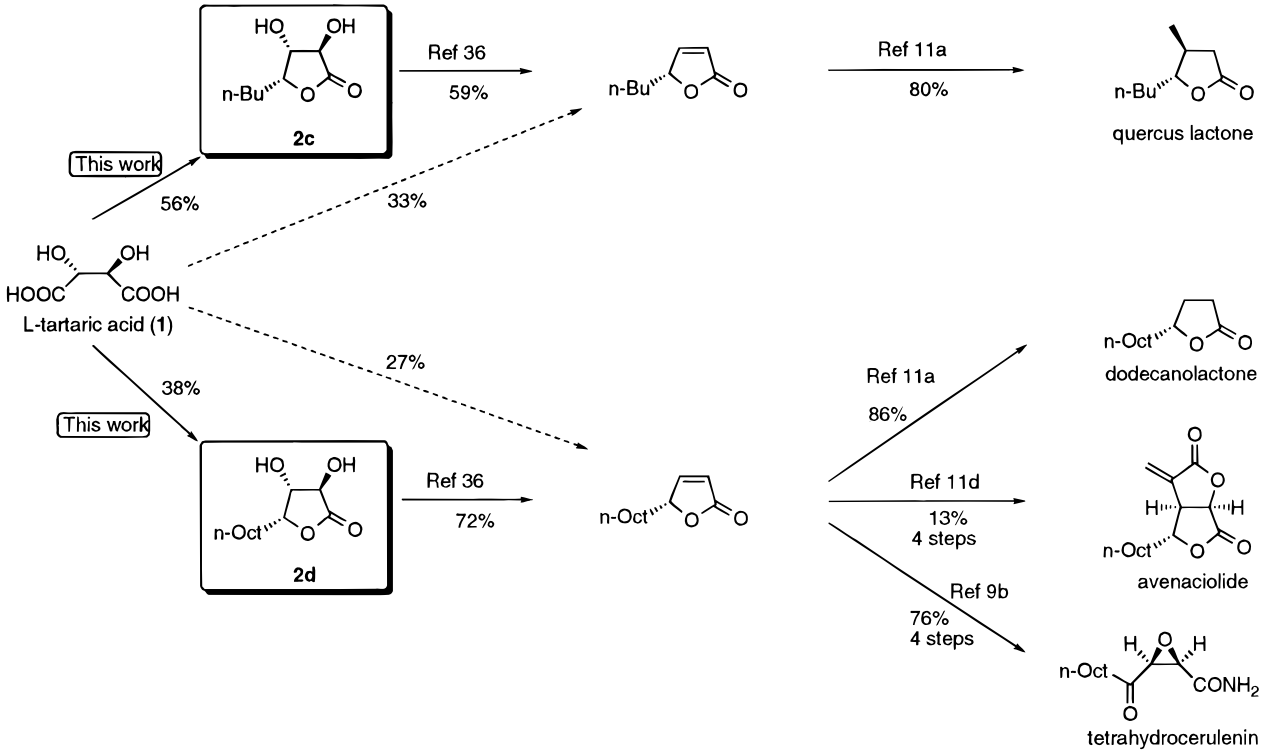
(27) Irradiation of the proton H4 led to a selective Overhauser effect on H2 (5%).



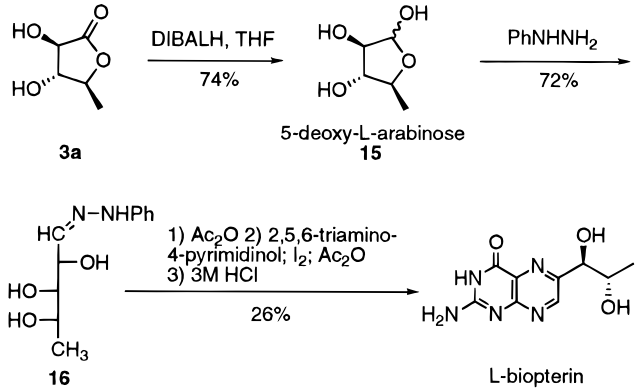
11d

(28) Cram, D. J.; Elhafez, F. A. A. *J. Am. Chem. Soc.* **1952**, *74*, 5828.
(29) Bartlett, P. A. *Tetrahedron* **1980**, 3.
(30) Chérest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, *18*, 2199.
(31) Torii, S.; Inokuchi, T.; Masatsugu, Y. *Bull. Chem. Soc. Jpn* **1985**, *58*, 3629.
(32) Quercus lactone is identified as a key aroma component of aged alcoholic beverages such as whisky, brandy, and wines.[3]
(33) Dodecanolactone is a defensive secretion of rove beetles.[9a]
(34) Avenaciolide is an antifungal agent first isolated from *Aspergillus avenaceus*.[11d]
(35) Tetrahydrocerulenin results of the catalytic hydrogenation of the natural cerulenin.[9b]
(36) Yoda, H.; Shirakawa, K.; Takabe, K. *Chem. Lett.* **1991**, 489.
(37) Rembold, H.; Gyure, W. L. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 1061.

Scheme 7



Scheme 8



DOPA,[38] melanine synthesis,[39] and tryptophan hydroxylation.[40] Thus, tetrahydrobiopterin has been proposed as a remedy for CNS diseases such as phenylketonuria, Parkinson's and Alzheimer's diseases, and depression.[41]

We recently described the first synthesis of L-biopterin from L-tartaric acid (**1**) *via* the γ-butyrolactone **3a** prepared in this work (Scheme 8).[42]

The key intermediate, 5-deoxy-L-arabinose (**15**), was obtained by reduction of the lactone **3a** with DIBALH.[42] L-Biopterin was prepared using slight modifications of literature procedures.[42,43] Treatment of lactol **15** with phenylhydrazine in MeOH gave phenylhydrazone **16**. This compound, after acetylation, was allowed to react with 2,5,6-triamino-4-pyrimidinol and then oxidized with I_2. Deprotection led to L-biopterin (Scheme 8). This new synthesis of biopterin exemplifies the strong potential for the construction of chiral compounds of the γ-butyrolactones prepared herein.

Conclusion

Starting from L-tartaric acid (**1**), we developed an efficient, general, and stereodivergent method of preparation of γ-alkylated γ-butyrolactones, epimers in the C4 position.

Two highly stereoselective reactions on carbonyl chirons allowed the obtention of these lactones with ee > 98%. These last compounds are precursors of biological molecules. Thus, formal syntheses of four natural products were realized, and a new total synthesis of L-biopterin was achieved.

In our strategy, alkyl groups were introduced by means of Grignard reagents. Thus, because of the wide availability of organometallic reagents, we think that this method could be extended to other optically pure γ-functionalized γ-butyrolactones such as β-angelica lactone, eldanolide, or chrysantemic acid.[44]

Experimental Section

Physical methods have been described.[42] Syntheses of compounds **3a**, **5**, **15**, **16**, and L-biopterin have already been

(38) (a) Nagatsu, T.; Levitt, M.; Udenfriend, S. *J. Biol. Chem.* **1964**, *239*, 2910. (b) Lloyd, T.; Weiner, N. *Mol. Pharmacol.* **1971**, *7*, 569.

(39) (a) Ziegler, I. *Z. Naturforsch.* **1963**, *18b*, 551. (b) Kokolis, N.; Ziegler, I. *Z. Naturforsch.* **1968**, *23b*, 860.

(40) (a) Gal, E. M.; Armstrong, J. C.; Ginsberg, B. *J. Neurochem.* **1966**, *13*, 643. (b) Hosoda, S.; Glick, D. *J. Biol. Chem.* **1966**, *241*, 192. (c) Noguchi, T.; Nishino, M.; Kido, R. *Biochem. J.* **1973**, *131*, 375.

(41) Nagatsu, T.; Matsuura, S.; Sugimoto, T. *Med. Res. Rev.* **1989**, *9*, 25.

(42) Fernandez, A. M.; Duhamel, L. *J. Org. Chem.* **1996**, *61*, 8698.

(43) (a) Schircks, B.; Bieri, J. H.; Viscontini, M. *Helv. Chim. Acta* **1985**, *68*, 1639. (b) Mori, K.; Kikuchi, H. *Liebigs Ann. Chem.* **1989**, 1267.

(44) These compounds have been prepared using lactones as synthetic intermediates. See, for example: (a) β-Angelica lactone: Camps, P.; Cardellah, J.; Corbera, J.; Font, J.; Ortuño, R. M.; Ponsati, O. *Tetrahedron* **1983**, *39*, 395. (b) Eldanolide: Vigneron, J. P.; Méric, R.; Larchevêque, M.; Debal, A.; Kunesch, G.; Zagatti, P.; Gallois, M. *Tetrahedron Lett.* **1982**, *23*, 5051. Vigneron, J. P.; Méric, R.; Larchevêque, M.; Debal, A.; Lallemand, J. Y.; Kunesch, G.; Zagatti, P.; Gallois, M. *Tetrahedron* **1984**, *40*, 3521. Ortuño, R. M.; Font, J.; Merce, R. *Tetrahedron* **1987**, *43*, 4497. Sarmah, B. K.; Barua, N. C. *Tetrahedron* **1993**, *49*, 2253. (c) Chrysantemic acid: Franck-Neumann, M.; Sedrati, M.; Vigneron, J. P.; Bloy, V. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 996. Mann, J.; Thomas, A. *Tetrahedron Lett.* **1986**, 3533.

described.[42] Acid chloride **6** was obtained following the literature procedures[16] in 87% yield (oil) from **1**. Coupling constants (J) are reported in Hz.

(2*R*,3*R*)-Methyl-2,3-dipivaloxy-3-[(2-pyridinylthio)carbonyl]propanoate (8). To acid chloride **6**[16] (10.0 g, 28.5 mmol) in THF (56 mL), at 0 °C, was added 2-mercaptopyridine (3.17 g, 28.5 mmol). After the mixture was stirred overnight at rt, THF was evaporated, and the residue was treated with Et_2O (56 mL) and then neutralized with a saturated $NaHCO_3$ solution. After extraction with Et_2O, the organic layer was dried and evaporated. The crude product was purified by chromatography on silica gel (PE/Et_2O 1/1) to give thioester **8** (11.5 g, 95%, oil): IR (neat) 1767, 1744, 1709 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.20 (s, 9H), 1.26 (s, 9H), 3.66 (s, 3H), 5.52 (d, 1H, J = 2.2), 5.89 (d, 1H, J = 2.2), 7.24 (dd, 1H, J = 5, 7.7), 7.48 (d, 1H, J = 7.8), 7.68 (td, 1H, J = 7.7, 1.9), 8.54 (dd, 1H, J = 4.9, 1.8); ^{13}C NMR ($CDCl_3$) δ 26.8, 38.7, 52.7, 70.9, 75.7, 123.9, 130.2, 137.4, 149.8, 150.5, 166.4, 176.2, 176.6, 193.8; MS (CI/NH_3) m/z 426 $[M + H]^+$; $[\alpha]^{26}_D$ +27.7 (*c* 3, $CHCl_3$). Anal. Calcd for $C_{20}H_{27}NO_7S$: C, 56.46; H, 6.49; N, 3.29. Found: C, 56.52; H, 6.46; N, 3.35.

Synthesis of Ketones 4. General Procedure. To a solution of thioester **8** (2.0 g, 4.7 mmol) in THF (56 mL) was added, under nitrogen, at the temperature *T*, the appropriate Grignard reagent (5.2 mmol). The reaction was followed by TLC until the starting material had disappeared. After the time *t*, the reaction mixture was hydrolyzed at the temperature *T* with a saturated NH_4Cl solution. After the mixture was warmed to rt, the organic layer was extracted twice with Et_2O, dried, filtered, and evaporated. The oil was purified by chromatography on silica gel (PE/Et_2O 90/10).

Note: the ketone **4a** was always present with dialkylated lactone **9a**, which was easily separated under the chromatographic conditions.

(2*R*,3*R*)-Methyl-2, 3-dipivaloxy-4-oxopentanoate (4a): CH_3MgBr 3 M in Et_2O (1.7 mL, 5.2 mmol); *T*, −15 °C; *t*, 45 min; yield 80%, oil; IR (neat) 1767, 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.20 (s, 9H), 1.23 (s, 9H), 2.16 (s, 3H), 3.70 (s, 3H), 5.51 (d, 1H, J = 2.4), 5,55 (d, 1H, J = 2.4); ^{13}C NMR ($CDCl_3$) δ 26.7, 27.0, 38.5, 52.5, 70.6, 76.3, 166.6, 176.7, 201.6; MS (CI/NH_3) m/z 331 $[M + H]^+$; $[\alpha]^{26}_D$ −10.0 (*c* 1.5, $CHCl_3$). Anal. Calcd for $C_{16}H_{26}O_7$: C, 58.17; H, 7.93. Found: C, 58.00; H, 7.30.

(2*R*,3*S*)-2,3-Dipivaloxy-4-dimethylbutyrolactone (9a): byproduct of **4a**; white solid, 5%; mp 63−66 °C; IR (neat) 1800, 1743 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.20 (s, 9H), 1.22 (s, 9H), 1.41 (s, 3H), 1.53 (s, 3H), 5.30 (d, 1H, J = 7.9), 5.60 (d, 1H, J = 8); ^{13}C NMR ($CDCl_3$) δ 22.5, 26.8, 27.1, 38.6, 38.7, 71.7, 77.3, 82.5, 168.1, 176.8, 177; MS (CI/*t*-BuH) m/z 315 $[M + H]^+$, 332 $[M + NH_4]^+$. Anal. Calcd for $C_{16}H_{26}O_6$: C, 61.15; H, 8.28. Found: C, 60.96; H, 8.48.

(2*R*,3*R*)-Methyl-2, 3-dipivaloxy-4-oxohexanoate (4b): EtMgBr 1 M in THF (5.2 mL, 5.2 mmol); *T*, −15 °C; *t*, 45 min; yield 90%, oil; IR (neat) 1769, 1741 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.97 (t, 3H, J = 7.2), 1.17 (s, 9H), 1.21 (s, 9H), 2.36 (dq, 1H, J = 18.8, 7.3), 2.54 (dq, 1H, J = 18.7, 7.2), 3.68 (s, 3H), 5.54 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 6.7, 26.7, 26.8, 32.3, 38.6, 38.7, 52.5, 70.8, 76.1, 166.8, 176.8, 176.9, 204.3; MS (CI/*t*-BuH) m/z 345 $[M + H]^+$; $[\alpha]^{23}_D$ +6.3 (*c* 3.5, $CHCl_3$). Anal. Calcd for $C_{17}H_{28}O_7$: C, 59.30; H, 8.20. Found: C, 59.40; H, 8.16.

(2*R*,3*R*)-Methyl-2, 3-dipivaloxy-4-oxooctanoate (4c): *n*-BuMgCl 2 M in THF (2.6 mL, 5.2 mmol); *T*, −15 °C; *t*, 45 min; yield 90%, oil; IR (neat) 1769, 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.86 (t, 3H, J = 7.2), 1.18 (s, 9H), 1.22 (s, 9H), 1.30 (m, 2H), 1.47 (m, 2H), 2.31 (dt, 1H, J = 17.9, 7.3), 2.46 (dt, 1H, J = 17.9, 7.3), 3.69 (s, 3H), 5.54 (d, 1H, J = 2.4), 5.57 (d, 1H, J = 2.4); ^{13}C NMR ($CDCl_3$) δ 13.5, 21.9, 24.6, 26.6, 38.4, 38.5, 52.3, 70.5, 76.0, 166.6, 176.5, 203.2; MS (CI/*t*-BuH) m/z 373 $[M + H]^+$; $[\alpha]^{20}_D$ −2.8 (*c* 1, $CHCl_3$). Anal. Calcd for $C_{19}H_{32}O_7$: C, 61.27; H, 8.66. Found: C, 61.32; H, 8.96.

(2*R*,3*R*)-Methyl-2, 3-dipivaloxy-4-oxododecanoate (4d): *n*-OctMgCl 2 M in THF (2.6 mL, 5.2 mmol); *T*, −5 °C; *t*, 75 min; yield 85%, oil; IR (neat) 1770, 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.77 (t, 3H, J = 6.8), 1.11−1.16 (m, 28H), 1.45 (m, 2H), 2.29 (dt, 1H, J = 17.9, 7.2), 2.44 (dt, 1H, J = 17.9, 7.3), 3.62 (s, 3H), 5.48 (d, 1H, J = 2.4), 5.50 (d, 1H, J = 2.4); ^{13}C NMR ($CDCl_3$) δ 13.8, 22.4, 22.6, 26.6, 28.8, 29.1, 31.6, 38.5, 38.6, 38.8, 52.4, 70.6, 76.1, 166.7, 176.6, 176.8, 203.3; MS (CI/*t*-BuH) m/z 429 $[M + H]^+$; $[\alpha]^{23}_D$ −3.0 (*c* 20.6, $CHCl_3$). Anal. Calcd for $C_{23}H_{40}O_7$: C, 64.49; H, 9.41. Found: C, 64.59; H, 9.42.

Reduction of Ketones 4 with $NaBH_4$. General Procedure. To a solution of ketone **4** (2 mmol) in MeOH (25 mL) at −70 °C was added, under nitrogen, $NaBH_4$ (1.1 equiv, 2.2 mmol, 84 mg). After the mixture was stirred at −70 °C, during *t*, until the starting material had disappeared (TLC), 3 M HCl was added until pH = 5 and then distilled water. The reaction mixture was then allowed to warm to rt. The solvents were removed by evaporation, the residue treated with ether and distilled water, and then the organic layer dried and evaporated. After purification on silica gel (PE/Et_2O 4/1), the single alcohols **12** were obtained in 80−88% yield. Enantiomeric purities were assumed according to NMR data.

Note: The workup must begin with an acidic treatment as described in order to avoid the formation of diol **i**.[22]

(2*R*,3*S*,4*R*)-Methyl-2,3-dipivaloxy-4-hydroxypentanoate (12a): *t*, 3 h 30 min; yield 80%, oil; IR (neat) 3524, 1738 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.15−1.18 (m, 21H), 2.45 (m, 1H), 3.64 (s, 3H), 3.95 (m, 1H), 5.09−5.15 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 18.9, 26.8, 26.9, 38.6, 38.9, 52.4, 66.7, 70.8, 74.7, 167.9, 177.3, 177.6; MS (CI/*t*-BuH) m/z 333 $[M + H]^+$; $[\alpha]^{23}_D$ −17.6 (*c* 1.2, $CHCl_3$). Anal. Calcd for $C_{16}H_{28}O_7$: C, 57.98; H, 8.49. Found: C, 58.08; H, 8.51.

Note: After the chromatography of alcohol **12a**, 10% of lactone **10a** was also isolated.

(2*R*,3*S*,4*R*)-Methyl-2,3-dipivaloxy-4-hydroxyhexanoate (12b): *t*, 1h; yield 85%, oil; IR (neat) 3538, 1734 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.94 (t, 3H, J = 7.3), 1.17 (s, 9H), 1.20 (s, 9H), 1.35−1.52 (m, 2H), 2.15−2.29 (m, 1H), 3.67 (s, 3H), 3.69−3.71 (m, 1H), 5.16 (dd, 2H, J = 3.6, 6.9), 5.21 (d, 1H, J = 3.7); ^{13}C NMR ($CDCl_3$) δ 9.8, 26.0, 26.8, 27.0, 38.6, 38.9, 52.4, 70.9, 72.0, 73.3, 168.0, 177.3, 177.5; MS (CI/*t*-BuH) m/z 347 $[M + H]^+$; $[\alpha]^{25}_D$ −10.4 (*c* 1.8, $CHCl_3$). Anal. Calcd for $C_{17}H_{30}O_7$: C, 58.96; H, 8.67. Found: C, 59.08; H, 8.90.

(2*R*,3*S*,4*R*)-Methyl-2,3-dipivaloxy-4-hydroxyoctanoate (12c): *t*, 45 min; yield 85%, oil; IR (neat) 3521, 1738 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.83 (t, 3H, J = 6.3), 1.15−1.21 (m, 22H), 1.29−1.34 (m, 2H), 2.35−2.45 (m, 1H), 3.66 (s, 3H), 3.72−3.79 (m, 1H), 5.20−5.25 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 13.8, 22.3, 26.8, 27.0, 27.4, 32.5, 38.6, 38.9, 52.4, 70.5, 70.9, 73.6, 168.0, 177.2, 177.5; MS (CI/*t*-BuH) m/z 375 $[M + H]^+$; $[\alpha]^{23}_D$ −8.5 (*c* 2.4, $CHCl_3$). Anal. Calcd for $C_{19}H_{34}O_7$: C, 60.94; H, 9.15. Found: C, 60.95; H, 9.00.

(2*R*,3*S*,4*R*)-Methyl-2,3-dipivaloxy-4-hydroxydodecanoate (12d): *t*, 75 min; yield 90%, oil; IR (neat) 3524, 1738 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.82 (t, 3H, J = 6.0), 1.17−1.21 (m, 30H), 1.31−1.40 (m, 2H), 2.10−2.13 (m, 1H), 3.67 (s, 3H), 3.71−3.77 (m, 1H), 5.15−5.20 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 14.0, 22.5, 25.2, 26.8, 27.0, 29.1, 29.3, 29.6, 31.7, 32.9, 38.7, 38.9, 52.4, 70.6, 70.9, 73.6, 168.6, 177.3, 177.5; MS (CI/*t*-BuH) m/z 431 $[M + H]^+$; $[\alpha]^{25}_D$ −9.2 (*c* 1.6, $CHCl_3$). Anal. Calcd for $C_{23}H_{42}O_7$: C, 64.16; H, 9.83. Found: C, 64.06; H, 10.07.

Lactonization Step. General Procedure. To a solution of alcohol **12** (1 mmol) in CH_2Cl_2 (15 mL) at rt was added TsOH (1 mmol, 190 mg). After the mixture was stirred for 4 h, distilled water (10 mL) was added. The aqueous solution was extracted with Et_2O. The combined organic layers were dried and evaporated. The lactones **10** were chromatographed on silica gel (PE/Et_2O 9/1) to give 90−97% yield. Crude lactones **10** can be used as such for the deprotection step. No epimeric lactone **11** can be detected by NMR spectroscopy.

(2*R*,3*S*,4*R*)-2,3-Dipivaloxy-4-methylbutyrolactone (10a): yield 97%; mp 115−117 °C; IR (neat) 1802, 1742 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.19 (s, 9H), 1.21 (s, 9H), 1.34 (d, 3H, J = 6.7), 4.96 (qd, 1H, J = 6.5, 6.5), 5.39 (dd, 1H, J = 6.5, 6.5), 5.43 (d, 1H, J = 6.6); ^{13}C NMR ($CDCl_3$) δ 15.0, 26.8, 38.6, 70.8, 72.9, 75.4, 169.0, 176.9, 177.1; MS (CI/*t*-BuH) m/z 301 $[M + H]^+$; $[\alpha]^{23}_D$ +67.3 (*c* 0.73, $CHCl_3$). Anal. Calcd for $C_{15}H_{24}O_6$: C, 59.98; H, 8.05. Found: C, 60.03; H, 8.10.

(2*R*,3*S*,4*R*)-2,3-Dipivaloxy-4-ethylbutyrolactone (10b): yield 95%; mp 66−68 °C; IR (neat) 1803, 1742 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.00 (t, 3H, J = 7.3), 1.14 (s, 9H), 1.16 (s, 9H), 1.63 (qd, 2H, J = 7.5, 5.7), 4.67 (td, 1H, J = 6.1, 7.7), 5.37 (d, 1H, J = 3.0), 5.39 (dd, 1H, J = 6.5, 16.2); ^{13}C NMR ($CDCl_3$) δ 9.7,

22.6, 26.8, 38.7, 71.1, 72.8, 80.3, 169.2, 176.4, 176.6; MS (CI/*t*-BuH) *m*/*z* 315 $[M + H]^+$; $[\alpha]^{22}_D$ +74.6 (*c* 0.80, $CHCl_3$). Anal. Calcd for $C_{16}H_{26}O_6$: C, 61.13; H, 8.34. Found: C, 61.20; H, 8.38.

(2*R*,3*S*,4*R*)-2,3-Dipivaloxy-4-butylbutyrolactone (10c): yield 95%; mp 30−33 °C; IR (neat) 1801, 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (t, 3H, *J* = 6.7), 1.20−1.23 (m, 20H), 1.29−1.36 (m, 2H), 1.53−1.61 (m, 2H), 4.77 (td, 1H, *J* = 6.0, 6.9), 5.42 (d, 1H, *J* = 6.1), 5.42 (dd, 1H, *J* = 6.5, 12.6); ^{13}C NMR ($CDCl_3$) δ 13.7, 22.2, 26.8, 27.2, 29.0, 38.6, 71.1, 72.8, 79.1, 169.3, 176.9, 177.2; MS (CI/*t*-BuH) *m*/*z* 343 $[M + H]^+$; $[\alpha]^{22}_D$ +75.0 (*c* 2.19, $CHCl_3$). Anal. Calcd for $C_{18}H_{30}O_6$: C, 63.13; H, 8.83. Found: C, 63.38; H, 9.08.

(2*R*,3*S*,4*R*)-2,3-Dipivaloxy-4-octylbutyrolactone (10d): yield 90%; mp 35−37 °C; IR (neat) 1803, 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.85 (t, 3H, *J* = 6.6), 1.18−1.30 (m, 30H), 1.52−1.63 (m, 2H), 4.77 (td, 1H, *J* = 5.7, 6.5), 5.41 (dd, 1H, *J* = 6.3, 12.5), 5.41 (d, 1H, *J* = 6.2); ^{13}C NMR ($CDCl_3$) δ 14.0, 22.5, 25.2, 26.8, 29.0, 29.2, 29.3, 31.7, 38.7, 71.1, 72.8, 79.2, 169.3, 176.9, 177.2; MS (CI/*t*-BuH) *m*/*z* 399 $[M + H]^+$; $[\alpha]^{23}_D$ +74.5 (*c* 0.66, $CHCl_3$). Anal. Calcd for $C_{22}H_{38}O_6$: C, 66.30; H, 9.61. Found: C, 66.41; H, 9.44.

Synthesis of Lactones 11. General Procedure. The appropriate Grignard reagent (15 mmol, 1.5 equiv) was added, at the temperature *T*, to a solution of aldehyde **5** (10 mmol, 1 equiv) in THF (70 mL). After being stirred at *T* for the time t_1, the mixture was warmed to rt during the time t_2 for lactonization step (TLC control). The mixture was cooled to 0 °C and hydrolyzed with a saturated NH_4Cl solution. THF was removed, and the residue was extracted with ether. The organic layer was dried ($MgSO_4$) and evaporated. The crude product **11** was isolated by chromatography on silica gel (PE/Et_2O 90/10) to give the lactones **11a**−**d** in 85−90% yield. No epimeric lactone **10** can be detected by NMR spectroscopy.

(2*R*,3*S*,4*S*)-2,3-Dipivaloxy-4-methylbutyrolactone (11a): MeMgBr 3 M in Et_2O (5 mL, 15 mmol); *T*, −70 °C (t_1, 12 h) then rt (t_2, 2 h); yield 88%; mp 65−69 °C; IR (neat) 1804, 1742 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.17 (s, 9H), 1.21 (s, 9H), 1.49 (d, 3H, *J* = 6.4), 4.42 (qd, 1H, *J* = 6.5, 6.5), 5.18 (dd, 1H, *J* = 7.1, 7.1), 5.48 (d, 1H, *J* = 7.3); ^{13}C NMR ($CDCl_3$) δ 18.6, 26.8, 38.6, 72.4, 76.3, 77.1, 168.8, 176.9, 177.3; MS (CI/*t*-BuH) *m*/*z* 301 $[M + H]^+$; $[\alpha]^{23}_D$ −21.9 (*c* 1.22, $CHCl_3$). Anal. Calcd for $C_{15}H_{24}O_6$: C, 59.98; H, 8.05. Found: C, 60.08; H, 7.97.

(2*R*,3*S*,4*S*)-2,3-Dipivaloxy-4-ethylbutyrolactone (11b): EtMgBr 1 M in THF (15 mL, 15 mmol); *T*, −50 °C (t_1, 3 h) then rt (t_2, 2 h): yield 85%; mp 59−63 °C; IR (neat) 1806, 1742 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.02 (t, 3H, *J* = 7.5), 1.18 (s, 9H), 1.22 (s, 9H), 1.81 (qd, 2H, *J* = 6.6, 6.6), 4.28 (td, 1H, *J* = 6.5, 6.8), 5.29 (dd, 1H, *J* = 7.2, 7.2), 5.49 (d, 1H, *J* = 7.3); ^{13}C NMR ($CDCl_3$) δ 8.9, 26.1, 26.8, 38.6, 72.6, 75.3, 80.5, 168.9, 176.9, 177.3; MS (CI/*t*-BuH) *m*/*z* 315 $[M + H]^+$; $[\alpha]^{20}_D$ −25.8 (*c* 0.52, $CHCl_3$). Anal. Calcd for $C_{16}H_{26}O_6$: C, 61.13; H, 8.34. Found: C, 61.33; H, 8.15.

(2*R*,3*S*,4*S*)-2,3-Dipivaloxy-4-butylbutyrolactone (11c): *n*-BuMgCl 2 M in THF (7.5 mL, 15 mmol); *T*, −25 °C (t_1, 2 h) then rt (t_2, 2 h); yield 90%, oil; IR (neat) 1808, 1742 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.89 (t, 3H, *J* = 6.9), 1.19−1.22 (m, 20H), 1.32−1.36 (m, 2H), 1.73−1.79 (m, 2H), 4.32 (td, 1H, *J* = 7.2, 5.6), 5.28 (dd, 1H, *J* = 7.2, 7.2), 5.48 (d, 1H, *J* = 7.3); ^{13}C NMR ($CDCl_3$) δ 13.7, 22.2, 26.6, 26.8, 32.8, 38.6, 72.5, 75.8, 79.4, 169, 176.9, 177.2; MS (CI/*t*-BuH) *m*/*z* 343 $[M + H]^+$; $[\alpha]^{20}_D$ −51.0 (*c* 0.1, $CHCl_3$). Anal. Calcd for $C_{18}H_{30}O_6$: C, 63.13; H, 8.83. Found: C, 63.36; H, 8.73.

(2*R*,3*S*,4*S*)-2,3-Dipivaloxy-4-octylbutyrolactone (11d): *n*-OctMgCl 2 M in THF (7.5 mL, 15 mmol); *T*, −25 °C (t_1, 1 h) then rt (t_2, 3 h); yield 90%, oil; IR (neat) 1810, 1746 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.85 (t, 3H, *J* = 6), 1.17−1.23 (m, 30H), 1.66−1.82 (m, 2H), 4.31 (td, 1H, *J* = 7, 5.9), 5.27 (dd, 1H, *J* = 7.2, 7.2), 5.48 (d, 1H, *J* = 7.3); ^{13}C NMR ($CDCl_3$) δ 14.0, 22.5, 24.6, 25.5, 26.8, 29.1, 29.2, 31.7, 33.1, 38.6, 72.5, 75.8, 79.4, 169, 176.9, 177.2; MS (CI/*t*-BuH) *m*/*z* 399 $[M + H]^+$; $[\alpha]^{20}_D$ −63.7 (*c* 0.92, $CHCl_3$). Anal. Calcd for $C_{22}H_{38}O_6$: C, 66.30; H, 9.61. Found: C, 66.36; H, 9.73.

Deprotection Step. General Procedure. To alcohols **12a**−**d** or lactones **10a** and **11a** (1 mmol) were added dioxane (12 mL) and 3 M HCl (24 mL). After the time *t* at reflux, the mixture was cooled to rt and then concentrated. The remaining solids were washed several times with hot AcOEt, and the washings were filtered, dried, and concentrated by azeotropic distillation with toluene. After purification on silica gel (PE/AcOEt 7/3), lactones **2a**−**d** and **3a** were obtained in high yields. Enantiomeric purities were assumed according to NMR data as well as comparison with literature data reported for compounds **2d** and **3a**.

(2*R*,3*S*,4*R*)-2,3-Dihydroxy-4-methylbutyrolactone (2a): *t*, 18 h; yield 80% from alcohol **12a**, 90% from the lactone **10a**, oil; IR (neat) 3379, 1774 cm^{-1}; ^1H NMR (CD_3OD) δ 1.34 (d, 3H, *J* = 6.7), 4.19−4.21 (m, 2H), 4.65−4.78 (m, 1H), 4.84 (s, 2H); ^{13}C NMR (CD_3OD) δ 14.8, 74.0, 75.0, 79.2, 177.2; MS (CI/*t*-BuH) *m*/*z* 133 $[M + H]^+$; $[\alpha]^{22}_D$ +77.2 (*c* 2.04, CH_3OH). Anal. Calcd for $C_5H_8O_4$: C, 45.46; H, 6.10. Found: C, 45.03; H, 6.34.

Note: We observed that the lactone **2a** was spontaneously epimerized at the C2 position, at −20 °C, after 3 days. Thus, it cannot be stored for more than several hours.

(2*R*,3*S*,4*R*)-2,3-Dihydroxy-4-ethylbutyrolactone (2b): *t*, 18 h; yield 85%, oil; IR (neat) 3414, 1771 cm^{-1}; ^1H NMR (CD_3OD) δ 1.02 (t, 3H, *J* = 7.5), 1.72 (m, 2H), 4.15 (d, 1H, *J* = 5.5), 4.21 (dd, 1H, *J* = 5.5, 11.0), 4.46 (td, 1H, *J* = 5.1, 9.2), 4.89 (s, 2H); ^{13}C NMR (CD_3OD) δ 10.3, 22.9, 74.4, 74.7, 84.7, 177.3; MS (CI/*t*-BuH) *m*/*z* 147 $[M + H]^+$; $[\alpha]^{21}_D$ +84.6 (*c* 1.02, CH_3OH). Anal. Calcd for $C_6H_{10}O_4$: C, 49.31; H, 6.90. Found: C, 49.52; H, 7.04.

(2*R*,3*S*,4*R*)-2,3-Dihydroxy-4-butylbutyrolactone (2c): *t*, 18 h; yield 88%; mp 74−76 °C; IR (neat) 3426, 1776 cm^{-1}; ^1H NMR (CD_3OD) δ 0.93 (t, 3H, *J* = 6.9), 1.35−1.85 (m, 6H), 4.14 (d, 1H, *J* = 3.7), 4.18 (dd, 1H, *J* = 5.5, 14.2), 4.53 (td, 1H, *J* = 4.9, 9.2), 4.83 (s, 2H); ^{13}C NMR (CD_3OD) δ 14.3, 23.5, 28.9, 29.5, 74.5, 74.8, 83.4, 177.4; MS (CI/*t*-BuH) *m*/*z* 157 $[M + H - H_2O]^+$, 175 $[M + H]^+$; $[\alpha]^{23}_D$ +91.5 (*c* 1.00, $CHCl_3$). Anal. Calcd for $C_8H_{14}O_4$: C, 55.16; H, 8.10. Found: C, 55.20; H, 8.07.

(2*R*,3*S*,4*R*)-2,3-Dihydroxy-4-octylbutyrolactone (2d):[7c,d] *t*, 48 h; yield 60%; mp 66−68 °C (lit.[7d] mp 68−70 °C); IR (neat) 3423, 1774 cm^{-1}; ^1H NMR (CD_3OD) δ 0.90 (t, 3H, *J* = 6.6), 1.21−1.85 (m, 14H), 4.15 (d, 1H, *J* = 3.8), 4.17 (dd, 1H, *J* = 5.3, 14.3), 4.54 (td, 1H, *J* = 5, 9), 4.85 (s, 2H); ^1H NMR ($CdCl_3$) δ 0.85 (t, 3H, *J* = 6), 1.20−1.50 (m, 12H), 1.7−1.9 (m, 2H), 3.73 (m, 2H), 4.43 (m, 1H), 4.49 (m, 2H); ^{13}C NMR (CD_3OD) δ 14.2, 23.7, 26.8, 29.8, 30.4, 30.6, 33.0, 74.6, 74.9, 83.5, 177.7; ^{13}C NMR ($CDCl_3$) δ 14 0, 22.6, 26.6, 28.9, 29.1, 29.3, 29.4, 31.8, 72.9, 73.7, 81.2, 175.8; MS (CI/*t*-BuH) *m*/*z* 231 $[M + H]^+$; $[\alpha]^{22}_D$ +71.5 (*c* 0.8, $CHCl_3$) [lit.[7d] $[\alpha]^{19}_D$ +71.9 (*c* 0.78, $CHCl_3$)]. Anal. Calcd for $C_{12}H_{22}O_4$: C, 62.58; H, 9.63. Found: C, 62.43; H, 9.86.

(2*R*,3*S*,4*S*)-2,3-Dihydroxy-4-methylbutyrolactone (3a):[31,45] *t*, 18 h; yield 90% from **11d**; 78% from **5** in one pot; mp 124−125 °C (lit.[45] mp 125 °C); IR (neat) 3366, 1748 cm^{-1}; ^1H NMR (CD_3OD) δ 1.41 (d, 3H, *J* = 6.2), 3.78 (dd, 1H, *J* = 8.8, 8.7), 4.17 (qd, 1H, *J* = 6.2, 8.3), 4.32 (d, 1H, *J* = 9), 4.82 (s, 2H); ^{13}C NMR (CD_3OD) δ 18.1, 75.4, 78.4, 80.5, 176.4; MS (CI/*t*-BuH) *m*/*z* 115 $[M + H - H_2O]^+$, 133 $[M + H]^+$; $[\alpha]^{21}_D$ −37.0 (*c* 1.10, EtOH) [lit.[31] enantiomer (2*S*,3*R*,4*R*) $[\alpha]^{13}_D$ +37.3 (c 1.01, EtOH)]. Anal. Calcd for $C_5H_8O_4$: C, 45.46; H, 6.10. Found: C, 45.64; H, 6.26.

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