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Enzymatic Kinetic Resolution of 5-Hydroxy-4-oxa-*endo*-tricyclo[5.2.1.$0^{2,6}$]dec-8-en-3-ones: A Useful Approach to D-Ring Synthons for Strigol Analogues with Remarkable Stereoselectivity

Jan Willem J. F. Thuring, Gerard H. L. Nefkens, Margreth A. Wegman, Antonius J. H. Klunder, and Binne Zwanenburg*

NSR-Center for Molecular Structure, Design and Synthesis, Department of Organic Chemistry, University of Nijmegen, Toernooiveld, 6525 ED Nijmegen, The Netherlands

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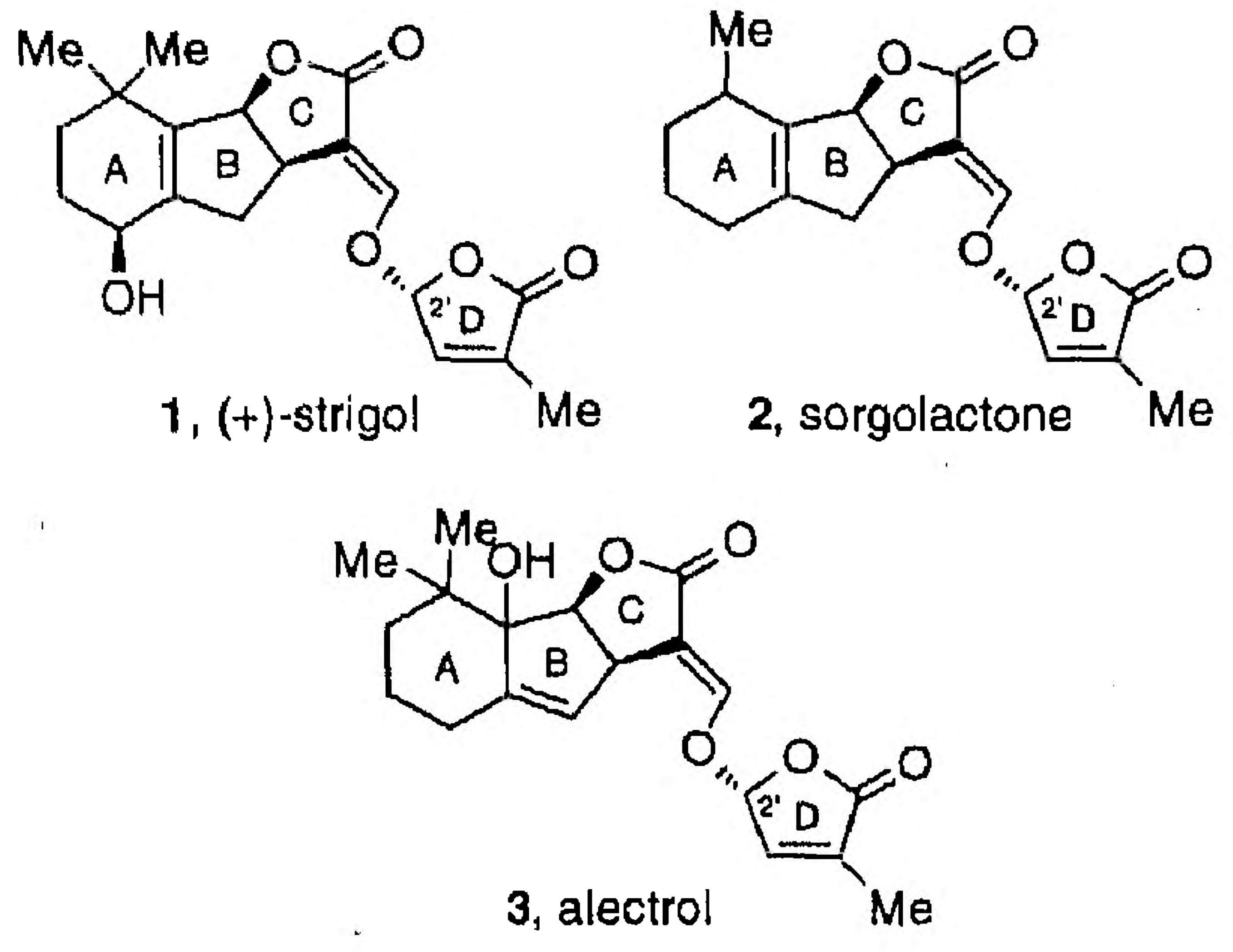
Racemic 5-hydroxy-4-oxa-*endo*-tricyclo[5.2.1.$0^{2,6}$]dec-8-en-3-one and its 2-methyl analogue were resolved employing a lipase-catalyzed acetylation reaction. The latter compound thus gave access to a homochiral D-ring synthon for strigolactones. The enzymatic acetylation reaction occurred with a remarkable inversion of configuration at C-5, through which it is possible to achieve a highly efficient asymmetric synthesis of 5-acetoxy-2(5*H*)-furanone.

(+)-Strigol (**1**) and some structurally related sesquiterpene lactones sorgolactone (**2**) and alectrol (**3**) are members of the "strigolactone" family,[1] which induce germination of seeds of the parasitic weeds *Striga* and *Orobanche*.[2−4]

These weeds cause severe damage to graminaceous and leguminous crops in tropical and semitropical areas in the eastern hemisphere.[5−7] As part of our interest in the (asymmetric) synthesis of the strigolactones and their synthetic analogues[8−12] we recently devised an asymmetric synthesis of the tricyclic *exo*-chloro lactone **4a** (Scheme 1),[13] which can be regarded as a homochiral D-ring synthon. This D-ring is a common structural feature of the strigolactones and is of prime importance for full biological activity. Even the absolute stereochemistry at C-2′ is essential for optimal stimulation of germination.[12,14,15]

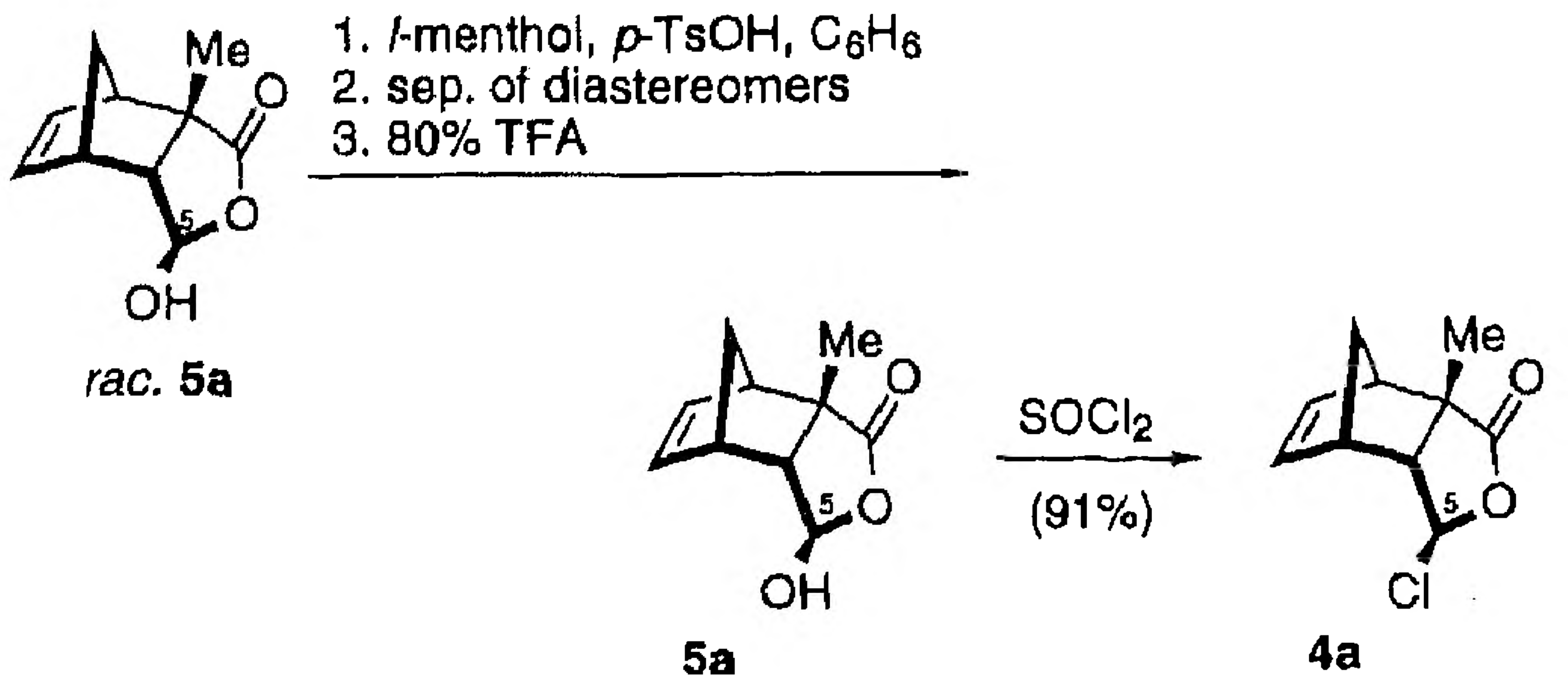
The key step in the synthesis of **4a** involves menthylation with *l*-menthol to give a 1:1 mixture of diastereomeric menthyl ethers, separation of the diastereomers, followed by acidic hydrolysis to give the enantiopure hydroxy lactone **5a**. This method provides access to both enantiomers of **5a** by choosing the appropiate enantiomer of menthol. However, the resolution is quite laborious since it requires two steps and a careful selective recrystallization. Moreover, 1 equiv of the chiral auxiliary is required. In order to circumvent these problems, a study was undertaken to improve the resolution, using an enzymatic approach.

Chart 1



1, (+)-strigol **2**, sorgolactone **3**, alectrol

Scheme 1



rac. **5a** **5a** **4a**

Enzymes currently find widespread use in synthetic organic chemistry.[16a−d] A prominent example of an enzymatic asymmetric transformation is the kinetic resolution of a racemic alcohol R*OH in the presence of

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[⊛] Abstract published in *Advance ACS Abstracts*, September 15, 1996.

(1) Butler, L. G. *ACS Symp. Ser.* **1995**, *582*, 158−168

(2) Siame, B. A.; Weerasuriya, Y; Wood, K.; Ejeta, G.; Butler, L. G. *J. Agric. Food Chem.* **1993**, *41*, 1486−1491.

(3) Hauck, C.; Müller, S.; Schildknecht, H. *J. Plant Physiol.* **1992**, *139*, 474−478.

(4) Müller, S.; Hauck, C.; Schildknecht, H. *J. Plant Growth Regul.* **1992**, *11*, 77−84.

(5) Musselman, L. J., Ed. Parasitic Weeds in Agriculture. *Striga*; CRC Press: Boca Raton, FL, 1987; Vol. I, 317 pp.

(6) Parker, C. Scope of the agronomic problems caused by *Orobanche* species. In *Proceedings of a workshop on biology and control of Orobanche*; Ter Borg, S. J., Ed.; LH/VPO: Wageningen, The Netherlands, 1986; pp 11−17.

(7) Parker, C.; Riches, C. R. *Parasitic Weeds of the World: Biology and Control*; CAB International: Wallingford, UK, 1993; 332 pp.

(8) Mangnus, E. M.; Zwanenburg, B. *Recl. Trav. Chim. Pays-Bas* **1992**, *111*, 155−159.

(9) Mangnus, E. M.; Zwanenburg, B. *J. Agric. Food Chem.* **1992**, *40*, 1066−1070.

(10) Mangnus, E. M.; van Vliet, L. A.; Vandenput, D. A. L.; Zwanenburg, B. *J. Agric. Food Chem.* **1992**, *40*, 1222−1229.

(11) Mangnus, E. M.; Dommerholt, F. J.; de Jong, R. L. P.; Zwanenburg, B. *J. Agric. Food Chem.* **1992**, *40*, 1230−1235.

(12) Mangnus, E. M.; Zwanenburg, B. *J. Agric. Food Chem.* **1992**, *40*, 697−700.

(13) Thuring, J. W. J. F.; Harren, F. J. M.; Nefkens, G. H. L.; Reuss, J.; Titulaer, G. T. M.; de Vries, H. S. M.; Zwanenburg, B. *Tetrahedron* **1995**, *51*, 5047−5056.

(14) Thuring, J. W. J. F.; Mangnus, E. M.; Zwanenburg B. Ethene production by seeds of *Striga hermonthica* induced by germination stimulants. In *Proceedings of the third international workshop on Orobanche and related Striga research*; Pieterse, A. H., Verkley, J. A. C., Ter Borg, S. J., Eds.; Royal Tropical Institute: Amsterdam, The Netherlands, 1994; pp 225−236.

(15) Bergmann, C.; Wegmann, K.; Frischmuth, K.; Samson, E.; Kranz, A.; Weigelt, D.; Koll, P.; Welzel, P., *J. Plant Physiol.* **1993**, *142*, 338−342.

S0022-3263(96)01022-5 CCC: $12.00

Scheme 2

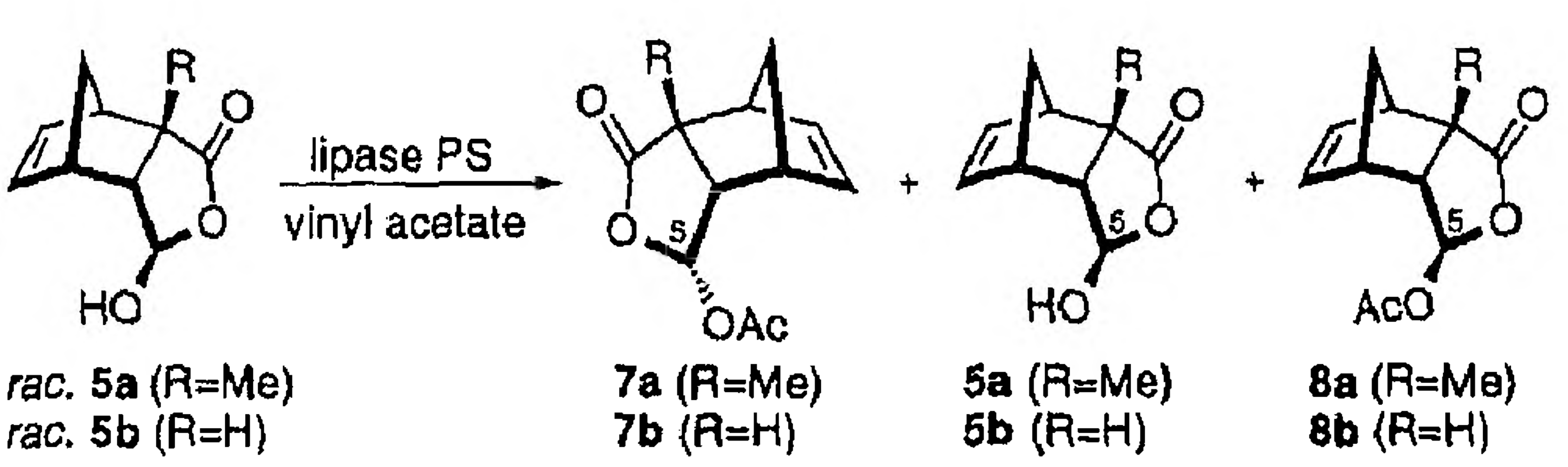


Table 1. Lipase PS-Catalyzed Transesterification of *endo*-Tricyclic Hydroxy Lactone *rac*-5a

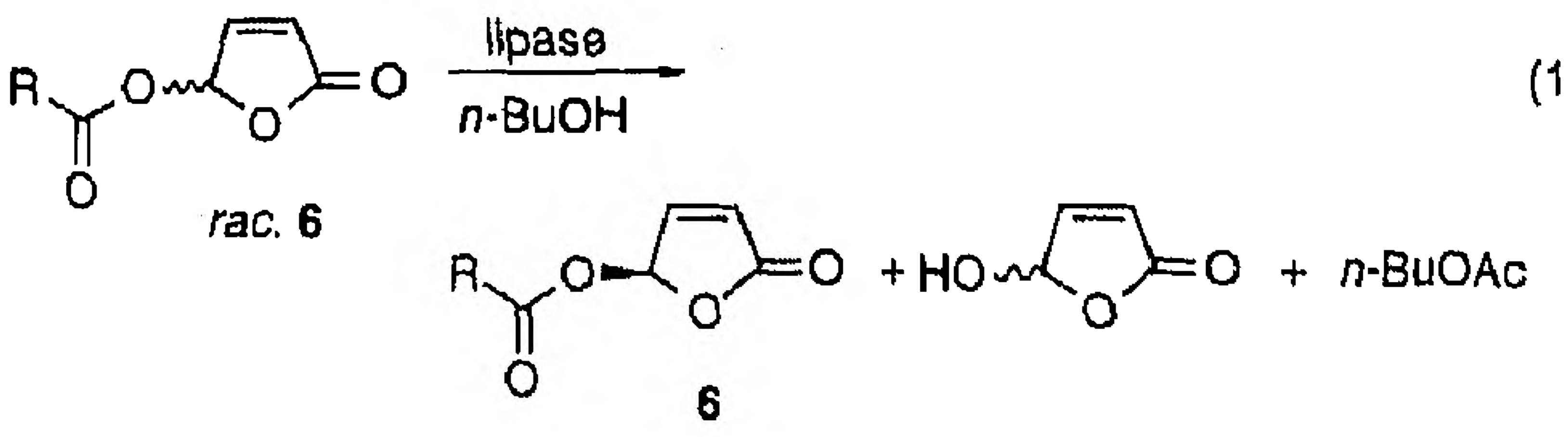
			product distribution (%)		
entry	time, h	conversion (%)	**7a** (% ee)	**5a** (% ee)	**8a**
1	22	30.8	30.2 (>90)	69.2 (41)	0.6
2	46	48.0	45.7 (87)	52.0 (79)	2.3
3	70	56.2	51.6 (87)	43.8 (85)	4.6

an acyl donor $R^2C(O)OR^3$, catalyzed by a lipase. The charm of this methodology lies in the facts that organic solvents can be used, workup is extremely simple, and a large variety of substrates is tolerated in this transformation. The application of enol esters as irreversible acyl donors[16b] makes this type of resolution even more attractive. In the present paper we describe the kinetic resolution of racemic *endo*-tricyclic hydroxy lactones **5** employing vinyl acetate as irreversible acyl donor, catalyzed by lipase PS.

Results and Discussion

Starting *endo*-tricyclic *exo*-hydroxy lactones **5** were obtained by standard literature procedures. Hydroxy lactone **5a** was prepared by a Diels–Alder reaction of citraconic anhydride and cyclopentadiene, followed by partial reduction according to the procedure of Canonne.[17] Hydroxy lactone **5b** was obtained by photooxidation of furfural[18] and subsequent Diels–Alder reaction with cyclopentadiene.

Kinetic Resolution. In a recent paper Kellogg *et al.* described the lipase-mediated transesterification of 5-acyloxy-2(5*H*)-furanones *rac*-**6** with 1-butanol resulting in ee's ranging from 68–98% (eq 1) with hitherto unknown stereochemistry.[19]



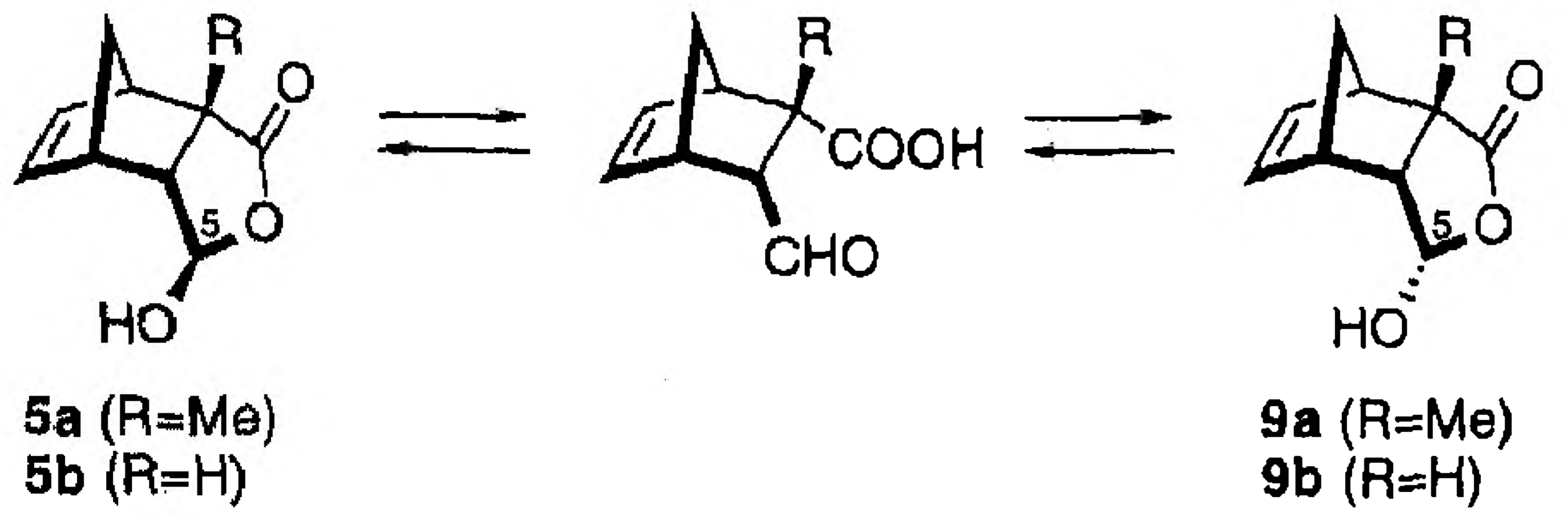
(1)

We have studied the irreversible acetylation of *endo*-tricyclic *exo*-hydroxy lactones **5** in the presence of vinyl acetate in dichloromethane catalyzed by lipase PS (Scheme 2). The results are collected in Tables 1 and 2.

As can be deduced from the data shown in Tables 1 and 2, the lipase PS-mediated acetylation of hydroxy lactones **5** is accomplished in good to excellent ee's. It should be emphasized that this conversion does not take place when other lipases were employed (lipase A, lipase R). Along with the *endo*-acetates **7a** and **7b**, *exo*-acetates **8a** and **8b** were formed in minor amounts (Tables 1 and 2). A striking observation is the fact that this reaction takes place with epimerization at C-5. The formation of the *endo*-acetates **7a** and **7b** could readily be deduced from ^{1}H-NMR analysis. The acetal proton H_5 of the *endo*-isomers **7a** and **7b** exhibited a doublet (^3J = 7 Hz for **7a** and 6 Hz for **7b**) at ca. 0.6 ppm lower field as compared to the corresponding *exo*-isomers (^3J = 1 Hz), which is in agreement with previous observations.[13] These results suggest that the reaction takes place via the thermodynamically unfavorable *endo*-hydroxy epimers **9**, which can be formed from the corresponding *exo*-isomers by *mutarotation* (eq 2). During NMR experiments in $CDCl_3$, we never observed the presence of the *endo*-epimers in the solution.

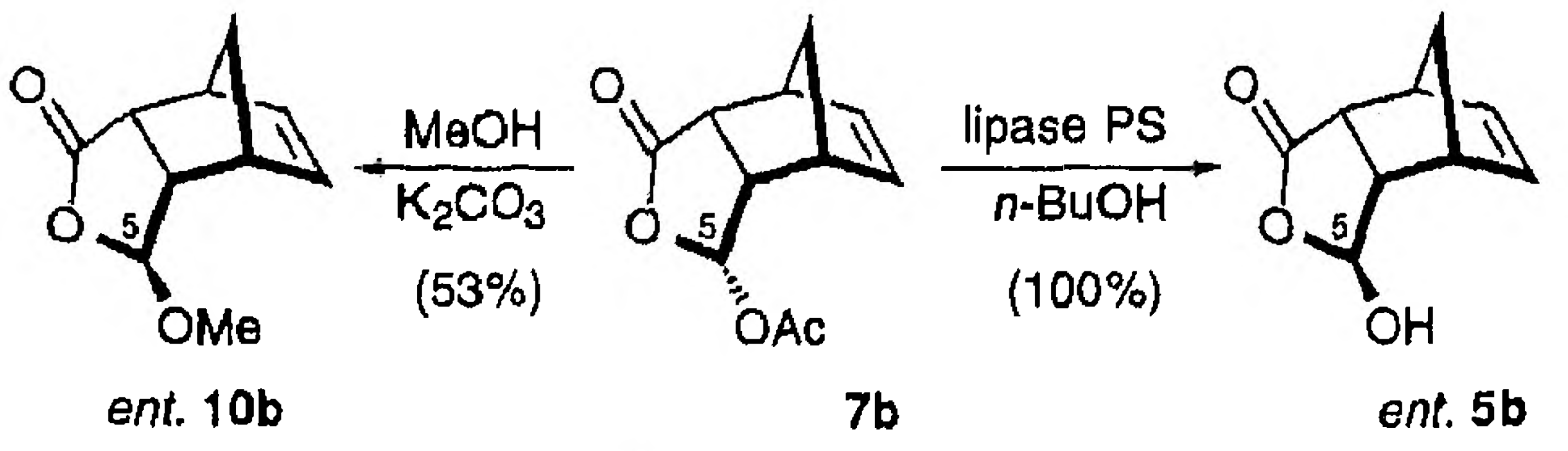
Table 2. Lipase PS-Catalyzed Transesterification of *endo*-Tricyclic Hydroxy Lactone *rac*-5b

			product distribution (%)		
entry	time, h	conversion (%)	**7b** (% ee)	**5b** (% ee)	**8b**
1	17	39.0	39.0 (>90)	61.0 (56)	0
2	47	53.5	50.0 (>90)	46.5 (>90)	3.5
3	17 days	60.8	45.2 (>90)	39.2 (>90)	15.6



(2)

It should be noted that it is not possible to obtain the *endo*-acetates by any other means. Acetylation reactions under conventional conditions, such as Ac_2O/pyridine or Ac_2O/*p*-TsOH, gave exclusively the *exo*-acetates **8**. In order to gain information about the existence of the *exo*/*endo* equilibrium (eq 2), we subjected the *endo*-acetate **7b** to a transesterification reaction. However, employing MeOH as a solvent in the presence of K_2CO_3 the expected *exo*-hydroxy lactone *ent*-**5b** was not obtained, but *exo*-methoxy lactone *ent*-**10b** was isolated as the main product (eq 3). Therefore, we switched to the enzymatic approach. Lipase PS-catalyzed transesterification in the presence of 10 equiv of *n*-BuOH in CH_2Cl_2 led to the exclusive formation of *exo*-hydroxy lactone *ent*-**5b** (eq 3). Again, no trace of *endo*-hydroxy lactone could be detected.



(3)

The results obtained with lipase PS-catalyzed acetylation of racemic hydroxy lactones **5** (Scheme 2) fit into a model in which only one enantiomer of the thermodynamically unfavorable *endo*-hydroxy lactones **9** is withdrawn from the *exo*/*endo* equilibrium (eq 2) to undergo a relatively fast enzymatic acetylation reaction. This sequence is an example of the *Curtin–Hammett* principle.[20] This remarkably large kinetic difference between

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[16] For reviews see: (a) Chen, C. S.; Sih, C. J. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 695–707. (b) Faber, K.; Riva, S. *Synthesis* **1992**, 895–910. (c) Boland, W.; Frössl, C.; Lorenz, M. *Synthesis* **1991**, 1049–1072. (d) Santaniello, E., Ferraboschi, P., Grisenti, P.; Manzocchi, A. *Chem. Rev.* **1992**, *92*, 1071–1140.

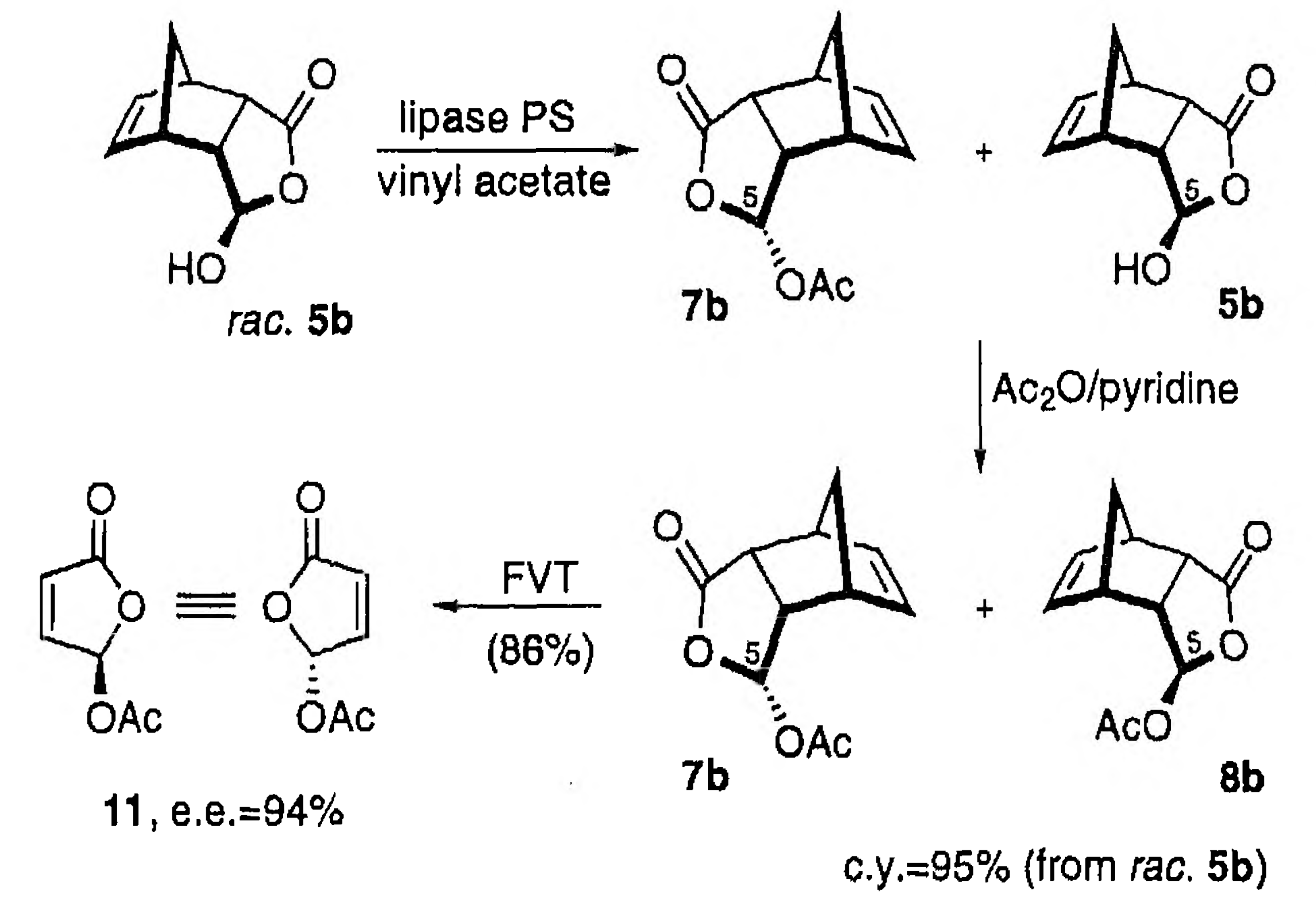
[17] Canonne, P.; Plamondon, J.; Akssira, M. *Tetrahedron* **1988**, *44*, 2903–2912.

[18] Yuste, F.; Sánchez-Obregón, R. *J. Org. Chem.* **1982**, *47*, 3665–3668.

[19] Deen van der, H.; Hof, R. P.; Oeveren van, A.; Feringa, B. L.; Kellogg, R. M. *Tetrahedron Lett.* **1994**, *35*, 8441–8444.

[20] Carey, F. A., Sundberg, R. J. *Advanced Organic Chemistry, Part A*, 3rd ed.; Plenum Press: New York, 1990; pp 215–216.

Scheme 3



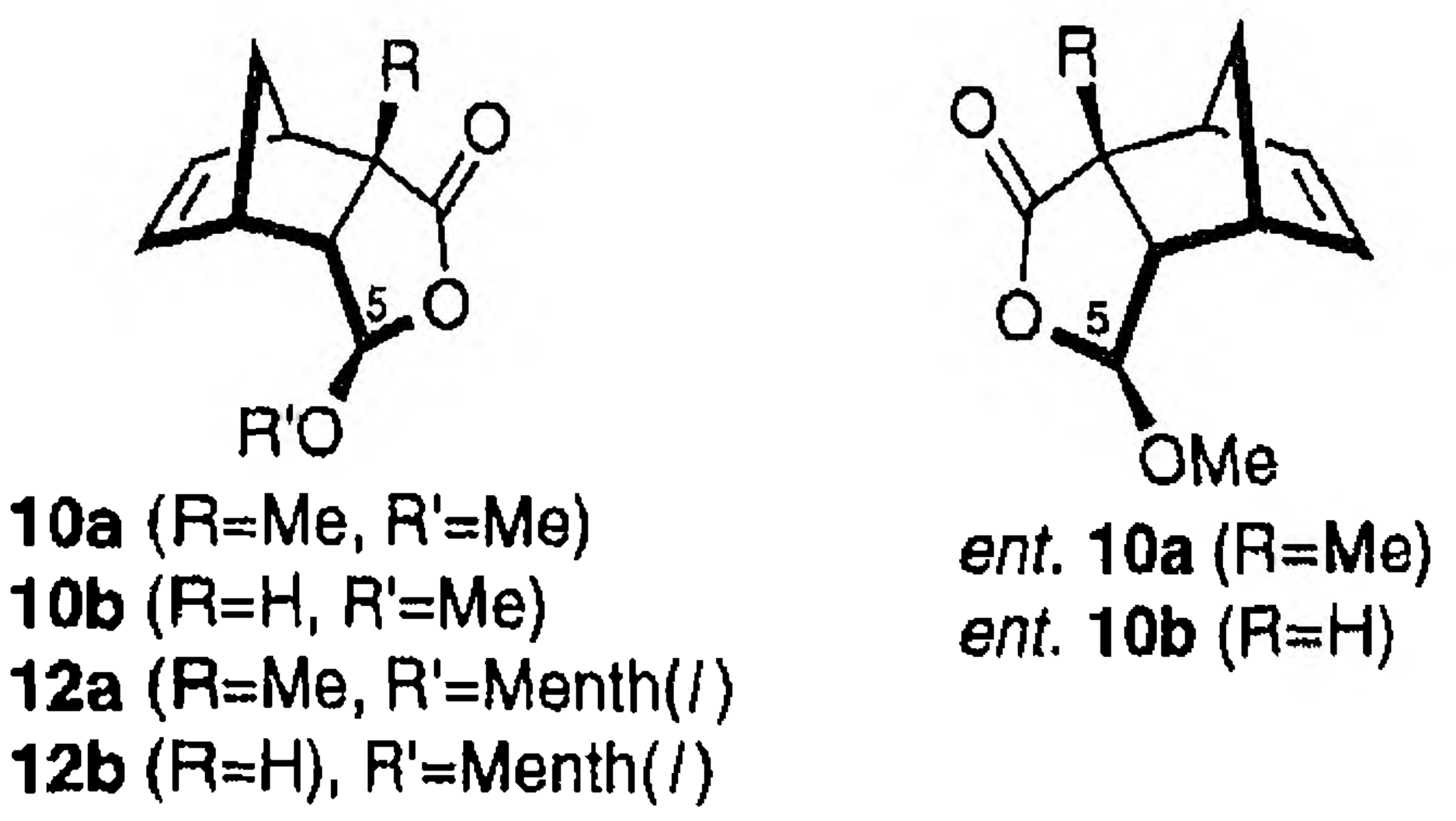
the *endo*- and *exo*-hydroxy lactones results in an excellent selectivity of product formation. It should be noted that in the absence of the lipase no conversion into **7a,b** or **8a,b** was observed even after 17 days. This implies that the formation of *exo*-acetates **8a,b** (*e.g.* Table 2, entry 3) is also catalyzed by the lipase, albeit in a much lower rate. The formation of the *exo*-acetates **8a** and **8b**, which are diastereomeric to the initially formed products **7a,b**, takes place via the *exo*-epimers **5a** and **5b**, respectively. This formation of diastereomers **7** and **8**, which is the ultimate result of the *exo*/*endo* equilibrium as depicted in eq 2, is quite unusual in kinetic resolutions.

The interesting finding shown in Scheme 2 can be advantageously utilized to achieve a sequence with full *chiral economy* (Scheme 3).in the following manner.

The crude mixture of **7b** and **5b**, obtained by kinetic resolution of *rac*-**5b** is acetylated under standard conditions to give the diastereomeric products **7b** and **8b**. Without further purification this mixture was subjected to a cycloreversion reaction, employing the technique of flash vacuum pyrolysis (FVT). This reaction led to the formation of one single isomer of 5-acetoxy-2(5*H*)-furanone **11**. This remarkable result can be rationalized by taking into account that a double stereodifferentiation has taken place. These results demonstrate the successful application of an enzymatic kinetic resolution of a racemic mixture, providing one single enantiomer without purification of any intermediate.

Determination of Enantiomeric Excess and Absolute Configuration. The ee's of the tricyclic hydroxy lactones **5a** and **5b** were established after menthylation with *l*-menthol to give the corresponding *l*-menthyloxy lactones **12a** and **12b** as a mixture of diastereomers with known absolute stereochemistry.[13,21] The de's could thus be determined by comparison of the relative intensities of the acetal H_5 proton signals in the ^{1}H-NMR spectrum. As there is no stereochemical preference in the menthylation reaction,[13] this derivatization allows the determination of the ee's of the hydroxy lactones **5**. Moreover, this derivatization to menthyl acetals **12** with known stereochemistry enables the unambigious assignment of the absolute stereochemistry as is shown (Scheme 2). Although effective, a more convenient procedure to determine the respective ee's involves the conversion of hydroxy lactones **5** and *endo*-acetoxy lactones **7** into the corresponding methyl acetals **10a,b** and *ent*-**10a,b**. These methylations occurred with complete *exo* selectivity in almost quantitative yields.

Chart 2



The ee's then were determined employing 400 MHz ^{1}H-NMR analysis in the presence of the chiral shift reagent $Eu(hfc)_3$ (1.5 equiv). In the case of methoxy lactones **10a** and *ent*-**10a** a difference of 0.03 ppm was observed for the α-methyl protons. On the other hand, the ee of methoxy lactone **10b**[22] was calculated on the basis of a 0.03 ppm difference of chemical shift of the acetal proton H_5 as compared to its enantiomer *ent*-**10b**. The determination of ee of acetoxy-2(5*H*)-furanone **11** was accomplished by comparison of the relative intensities of the CH_3 signals in the ^{1}H-NMR spectrum using 0.4 equiv of $Eu(hfc)_3$, which resulted in a downfield shift of approximately 0.8 ppm and a difference of 0.16 ppm for both enantiomers. On the basis of the above assignment of the absolute stereochemistry the levorotatory 5-acetoxy-2(5*H*)-furanone **11**, obtained by Kellogg *et al.* according to eq 1,[19] can be assigned as 5(*R*).

Conclusion

Lipase PS-mediated acetylation proved to be a simple, highly efficient method for the kinetic resolution of racemic tricyclic hydroxy lactones **5**. Employing this methodology it is possible to synthesize both enantiomers of *exo*-chloro lactones **4a**. These optically active latent butenolides are useful synthons for the preparation of homochiral strigolactones.[13] The kinetic resolution was accompanied with a remarkable epimerization, which could be used to demonstrate the synthesis of enantiopure 5-acetoxy-2(5*H*)-furanone **11** with optimal "chiral economy".

Experimental Section

General. For general methods and instrumentation, see ref 13. GC-MS spectra were run on a Varian Saturn 2 GC-MS ion-trap system. Separation was carried out on a fused-silica capillary column (DB-5, 30 m × 0.25 mm). Helium was used as carrier gas, and electron impact (EI) was used as ionization mode. Lipase PS was obtained from Amano as a gift.

General Procedure for the Enzymatic Kinetic Resolution of the Tricyclic Hydroxy Lactones *rac*-5a and *rac*-5b. To a solution containing *exo*-hydroxy tricyclic lactone *rac*-**5a**[17] (500 mg, 2.79 mmol) and vinyl acetate (2.57 mL, 27.9 mmol) in CH_2Cl_2 (25 mL) were added lipase PS (1.0 g) and powdered 4A molecular sieves (0.5 g). The suspension was stirred vigorously at room temperature. At given intervals (Tables 1 and 2) samples were taken (3 mL) and filtered over hyflo. The hyflo was washed with CH_2Cl_2, and the crude mixture was analyzed by 100 MHz ^{1}H-NMR ($CDCl_3$) for conversion. Purification by chromatography (SiO_2, hexane/ethyl acetate 3:1) afforded *endo*-acetate **7a** as a white solid and *exo*-alcohol **5a** as a white solid, which were analyzed for ee (*vide infra*).

Enantiomeric Excess Determination. The hydroxy lactones **5a** and **5b** were transformed into the corresponding

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(21) de Jong, J. C.; van Bolhuis, F.; Feringa, B. L. *Tetrahedron Asymmetry* **1991**, *2*, 1247–1262.

(22) Farina, F.; Martin, M. V.; Paredes, M. C.; Ortega, M. C.; Tito, A., *Heterocycles* **1984**, *22*, 1733–1739

l-menthyl ethers **12**.[13,21] Alternatively, **5a** and **5b** were converted into the corresponding *exo*-methoxy lactones **10a**, **10b** and subsequently analyzed by 400 MHz ^{1}H-NMR (CDCl$_3$) in the presence of ca. 1.5 equiv of Eu(hfc)$_3$ (*vide infra*). Similarly, *endo*-acetates **7a** and **7b** were methylated to give *ent*-**10a** and *ent*-**10b**, respectively (*vide infra*), which were analyzed for ee in the same manner.

5(*R*)-Acetoxy-2(*R*)-methyl-4-oxa-*endo*-tricyclo[5.2.1.0^{2,6}]dec-8-en-3-one (7a) and 5(*R*)-hydroxy-2(*S*)-methyl-4-oxa-*endo*-tricyclo[5.2.1.0^{2,6}]dec-8-en-3-one (5a). These compounds were synthesized according to the general procedure starting from *rac*-**5a**[17] (3.00 g, 16.7 mmol). The reaction was stopped after 73 h. Purification by chromatography (SiO$_2$, hexane/ethyl acetate 3:1) gave **7a** (1.28 g, 34%) as a white solid and **5a** (1.18 g, 39%) as a white solid. Analytical samples of **5a** and **7a** were obtained by recrystallization from hexane/ethyl acetate.

7a: mp 98.5–101.5 °C; $[\alpha]_D$ −88.4° (*c* 0.4, CH$_2$Cl$_2$); ^{1}H-NMR (CDCl$_3$, 100 MHz): δ 1.54 (s, 3H), 1.69 (m, 2H), 2.15 (s, 3H), 2.85 (m, 1H), 2.87 (dd, J = 3.9, 7.0 Hz, 1H), 3.04 (m, 1H), 6.26 (m, 2H), 6.50 (d, J = 7.0 Hz, 1H); GC-MS (EI, *m/z*, rel int (%)): 163 (M$^+$ − OAc, 90.4), 157 (1.7), 152 (23.4), 97 (13.6), 91 (16.9), 66 (100). Anal. Calcd for C$_{12}$H$_{14}$O$_4$: C, 64.85; H, 6.35. Found: C, 65.28; H, 6.31.

5a: All analytical data (Mp, $[\alpha]_D$, ^{1}H-NMR, and mass data) were in complete agreement with those reported previously.[13]

5(*R*)-Acetoxy-4-oxa-*endo*-tricyclo[5.2.1.0^{2,6}]dec-8-en-3-one (7b) and 5(*R*)-Hydroxy-4-oxa-*endo*-tricyclo[5.2.1.0^{2,6}]dec-8-en-3-one (5b). These compounds were synthesized according to the general procedure starting from *rac*-**5b**[17] (3.00 g, 18.1 mmol). The reaction was stopped after 46 h. Purification by chromatography (SiO$_2$, hexane/ethyl acetate 3:1) gave **7b** (1.65 g, 44%) as a white solid and **5b** (1.41 g, 47%) as a white solid. Analytical samples of **5b** and **7b** were obtained by recrystallization from hexane/ethyl acetate.

7b: mp 116.5–118 °C; $[\alpha]_D$ −126.0° (*c* 1.0, CH$_2$Cl$_2$); ^{1}H-NMR (CDCl$_3$, 100 MHz): δ 1.47 (dt, J = 1.0 Hz, 9.0 Hz, 1H), 1.65 (dt, J = 1.0 Hz, 9.0 Hz, 1H), 2.15 (s, 3H), 3.11 (m, 1H), 3.36 (m, 3H), 6.25 (m, 2H), 6.48 (d, J = 6.0 Hz, 1H); GC-MS (EI, *m/z*, rel int (%)): 166 (M$^+$ + 1 − Ac, 12.2), 149 (M$^+$ − OAc, 49.2), 137 (12.2), 91 (42.3), 83 (9.1), 66 (100). Anal. Calcd for C$_{11}$H$_{12}$O$_4$: C, 63.45; H, 5.81. Found: C, 63.55; H, 5.79.

5b: mp 134–136.5 °C; $[\alpha]_D$ +53.2° (*c* 0.2, CH$_2$Cl$_2$); ^{1}H-NMR (CDCl$_3$, 100 MHz): δ 1.37 (dt, J = 1.0 Hz, 8.5 Hz, 1H), 1.56 (dt, J = 1.0 Hz, 8.5 Hz, 1H), 2.86 (m, 1H), 3.33 (m, 3H), 4.83 (br s, 1H), 5.16 (br s, 1H), 6.14 (m, 2H); GC-MS (EI, *m/z*, rel int (%)): 167 (M$^+$ + 1, 1.9), 149 (2.0), 91 (29.3), 83 (3.1), 66 (100). Anal. Calcd for C$_9$H$_{10}$O$_3$: C, 65.05; H, 6.07. Found: C, 64.97; H, 6.00.

5(*S*)-Hydroxy-4-oxa-*endo*-tricyclo[5.2.1.0^{2,6}]dec-8-en-3-one (*ent*-5b). A solution containing **7b** (50 mg, 0.24 mmol) and *n*-BuOH (0.22 mL, 24 mmol) in CH$_2$Cl$_2$ (3 mL) were treated with lipase PS (100 mg) and powdered 4A molecular sieves (50 mg). The suspension was stirred vigorously at room temperature. After 24 h the suspension was filtered over hyflo and washed with CH$_2$Cl$_2$, and the filtrate was concentrated *in vacuo*. Yield 39.0 mg, 98% of pure *ent*-**5b** as a white solid. An analytical sample was obtained by recrystallization from hexane/ethyl acetate. Mp 130.5–131.5 °C; $[\alpha]_D$ −48.6° (*c* 0.2, CH$_2$Cl$_2$); ^{1}H-NMR and mass data were the same as for compound **5b**.

Racemic *exo*-5-Methoxy-2-methyl-4-oxa-*endo*-tricyclo[5.2.1.0^{2,6}]dec-8-en-3-one (*rac*-10a). For determination of ee of 5(*R*)-hydroxy lactone **5a**. *rac*-**5a** (50 mg, 0.28 mmol) was treated with methanol (2 mL) and 1 drop of thionyl chloride. The solution was stirred for 30 min and concentrated *in vacuo* to give pure *rac*-**10a** (53.4 mg, 96%) as a white solid: mp 86.5–89.5 °C; ^{1}H-NMR (CDCl$_3$, 400 MHz): δ 1.45 (s, 3H), 1.59 (m, 2H), 2.40 (dd, J = 1.0, 4.2 Hz, 1H), 2.75 (m, 1H), 3.05 (m, 1H), 3.36 (s, 3H), 4.66 (d, J = 1.0 Hz, 1H), 6.10 (m, 1H), 6.19 (m, 1H). Addition of 1.5 equiv of the chiral shift reagent Eu(hfc)$_3$ gave a splitting of the α-methyl signal of 0.03 ppm (1.07 ppm downfield shift). GC-MS (EI, *m/z*, rel int (%)): 195 (M$^+$ + 1, 59.0), 163 (10.4), 135 (15.2), 129 (39.4), 97 (20.1), 91 (26.9), 66 (100). Anal. Calcd for C$_{11}$H$_{14}$O$_3$: C, 68.02; H, 7.26. Found: C, 67.80; H, 7.19.

5(*S*)-Methoxy-2(*R*)-methyl-4-oxa-*endo*-tricyclo[5.2.1.0^{2,6}]dec-8-en-3-one (*ent*-10a). For determination of ee of *endo*-5(*R*)-acetoxy lactone **7a**. A solution of **7a** (25 mg, 0.11 mmol) in methanol (2 mL) was treated with 1 drop of thionyl chloride. The solution was stirred for 30 min and concentrated *in vacuo* to give pure *ent*-**10a** (21.1 mg, 97%), which was analyzed for ee as described for *rac*-**10a**.

Racemic *exo*-5-Methoxy-4-oxa-*endo*-tricyclo[5.2.1.0^{2,6}]dec-8-en-3-one (*rac*-10b).[22] For determination of ee of 5(*R*)-hydroxy lactone **5b**. A solution of *rac*-**5b** (50 mg, 0.31 mmol) in methanol (2 mL) was treated with 1 drop of thionyl chloride. The solution was stirred for 30 min and concentrated *in vacuo* to give crude *rac*-**10b**, which was not sufficiently pure for ee determination. Purification by chromatography (SiO$_2$, hexane/ethyl acetate 9:1) gave pure *rac*-**10b** (47.2 mg, 84%) as a white solid: mp 54.5–55.5 °C; ^{1}H-NMR (CDCl$_3$, 400 MHz): δ 1.44 (dt, J = 1.0 Hz, 8.6 Hz, 1H), 1.62 (dt, J = 1.0 Hz, 8.6 Hz, 1H), 2.91 (m, 1H), 3.19 (m, 1H), 3.31 (m, 2H), 3.43 (s, 3H), 4.79 (d, J = 1.1 Hz, 1H), 6.20 (m, 1H), 6.25 (m, 1H). Addition of 1.5 equiv of the chiral shift reagent Eu(hfc)$_3$ gave a splitting of the signal of the acetal proton H$_5$ of 0.03 ppm (1.37 ppm downfield shift). GC-MS (EI, *m/z*, rel int (%)): 181 (M$^+$ + 1, 10.7), 149 (12.6), 121 (14.4), 115 (9.4), 91 (54.6), 83 (15.3), 66 (100). Anal. Calcd for C$_{10}$H$_{12}$O$_3$: C, 66.65; H, 6.71. Found: C, 66.12; H, 6.62.

5(*S*)-Methoxy-4-oxa-*endo*-tricyclo[5.2.1.0^{2,6}]dec-8-en-3-one (*ent*-10b). For determination of ee of *endo*-5(*R*)-acetoxy lactone **7b**. This compound was prepared from **7b** (40 mg, 0.19 mmol) in the same way as described for the synthesis of *ent*-**10a**. Yield after chromatography (SiO$_2$, hexane/ethyl acetate 9:1) 28.2 mg, 83%. The ee was determined according to the procedure as described for *rac*-**10b**.

Racemic *exo*-5-Acetoxy-2-methyl-4-oxa-*endo*-tricyclo[5.2.1.0^{2,6}]dec-8-en-3-one (*rac*-8a). *rac*-**5a** (100 mg, 0.56 mmol) was dissolved in pyridine/acetic anhydride 2:1 v/v (1 mL) and stirred for 17 h at room temperature. The solvents were removed *in vacuo*, and the residue was coevaporated with toluene. Yield 121.8 mg, 98% of pure *rac*-**8a** as a colorless oil: ^{1}H-NMR (CDCl$_3$, 100 MHz): δ 1.50 (s, 3H), 1.62 (m, 2H), 2.04 (s, 3H), 2.50 (dd, J = 0.9, 4.2 Hz, 1H), 2.80 (m, 1H), 3.12 (m, 1H), 5.87 (d, J = 0.9 Hz, 1H), 6.19 (m, 2H), GC-MS (EI, *m/z*, rel int (%)): 163 (M$^+$ − OAc, 36.3), 157 (3.0), 97 (18.2), 91 (11.5), 66 (100); HRMS/EI: *m/z* calcd for C$_{12}$H$_{14}$O$_4$: 222.0892. Found 222.08931 ± 0.00088.

Racemic *exo*-5-Acetoxy-4-oxa-*endo*-tricyclo[5.2.1.0^{2,6}]dec-8-en-3-one (*rac*-8b). This compound was prepared from *rac*-**5b** (100 mg, 0.60 mmol) in the same way as described for the synthesis of *rac*-**8a**. Purification by chromatography (SiO$_2$, hexane/ethyl acetate 3:1) afforded *rac*-**8b** (119.8 mg, 87%) as a white solid. An analytically pure sample was obtained by recrystallization from hexane/ethyl acetate: mp 82.5–84 °C; ^{1}H-NMR (CDCl$_3$, 100 MHz): δ 1.39 (dt, J = 1.0 Hz, 8.7 Hz, 1H), 1.60 (dt, J = 1.0 Hz, 8.7 Hz, 1H), 2.03 (s, 3H), 2.96 (m, 1H), 3.25 (m, 3H), 5.86 (d, J = 1.2 Hz, 1H), 6.19 (m, 2H); GC-MS (EI, *m/z*, rel int (%)): 149 (M$^+$ − OAc, 10.2), 143 (1.6), 91 (23.6), 83 (11.6), 66 (100). Anal. Calcd for C$_{11}$H$_{12}$O$_4$: C, 63.45; H, 5.81. Found: C, 63.50; H, 5.79.

5(*R*)-Acetoxy-2(*S*)-methyl-4-oxa-*endo*-tricyclo[5.2.1.0^{2,6}]dec-8-en-3-one (8a). This compound was prepared from **5a** (100 mg, 0.56 mmol) in the same way as described for the synthesis of *rac*-**8a**. Yield 123.1 mg, 99% of **8a** as a colorless oil: $[\alpha]_D$ −79.3° (*c* 0.4, CH$_2$Cl$_2$). ^{1}H-NMR and mass data were the same as for compound *rac*-**8a**.

5(*R*)-Acetoxy-4-oxa-*endo*-tricyclo[5.2.1.0^{2,6}]dec-8-en-3-one (8b). This compound was prepared from **5b** (100 mg, 0.60 mmol) in the same way as described for the synthesis of *rac*-**8b**. Yield 119.8 mg, 87% of **8b** as a white solid. An analytically pure sample was obtained by recrystallization from hexane/ethyl acetate: mp 84–86.5 °C; $[\alpha]_D$ −27.2° (*c* 0.4, CH$_2$Cl$_2$). ^{1}H-NMR and mass data were the same as for compound *rac*-**8b**.

5(*R*)-Acetoxy-2(5*H*)-furanone (11). Flash vacuum thermolysis of **7b** (52.4 mg, 0.25 mmol) [sample temp: 80 °C; oven temp: 500 °C; cold trap temp: −78 °C; pressure: 5 × 10^{-2} mbar] provided pure **11** (32.7 mg, 92%) as a colorless oil: $[\alpha]_D$ −30.9° (*c* 0.7, CH$_2$Cl$_2$); ^{1}H-NMR data were the same as reported for *rac*-**11**.[23] Addition of Eu(hfc)$_3$ (0.4 equiv) gave a separation of CH$_3$ signals amounting 0.16 ppm for the corresponding enantiomers (0.8 ppm downfield shift), ee 94%.

The same compound **11** was obtained by FVT [sample temp: 120 °C; oven temp: 500 °C; cold trap temp: −78 °C; pressure: 5×10^{-2} mbar] starting from a 1:1 mixture of diastereomeric acetates **7b** and **8b** (110 mg, 0.53 mmol). Yield 64.9 mg, 86% as a colorless oil. $[\alpha]_D$ −34.2° (*c* 0.5, CH$_2$Cl$_2$), ee 94%.

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Supporting Information Available: Copies of ^{1}H NMR spectra of *rac*-**8a**, *rac*-**8b**, **7a**, **7b** (4 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.

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[23] Nagao, Y.; Dai, W.; Ochiai, M.; Shiro, M. *J. Org. Chem.* **1989**, *54*, 5211−5217.