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Preparation of optically active (acyloxy)alkyl esters from optically active *O*-acyl-α-hydroxy acids

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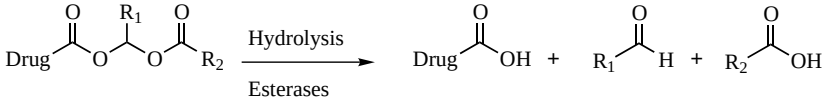
Abstract—(Acyloxy)alkyl esters are commonly employed as prodrugs of carboxylic acid containing compounds. Several optically active (acyloxy)alkyl esters are prepared from a coupling and rearrangement reaction between optically active *O*-acyl-α-hydroxy acids and 3-chloroperoxybenzoic acid mediated by diisopropylcarbodiimide. The effect of temperature and solvent on the reaction is discussed. An application of the reaction to prepare a prodrug form of ibuprofen is described.

(Acyloxy)alkyl esters **1** have been widely used as prodrugs of carboxylic acid containing compounds.[1] Diester **1** can undergo intracellular esterase catalyzed hydrolysis to the parent drug carboxylic acid **2**, as well as byproducts aldehyde **3** and acid **4** (Scheme 1). Examples of clinically approved drugs that contain the (acyloxy)alkyl ester prodrug moiety include antibiotic cefuroxime axetil (**5**),[2] and non-steroidal anti-inflammatory flurbiprofen axetil (**6**)[3] (Fig. 1). Compounds **5** and **6** are marketed as a mixture of epimers at the chiral center in the prodrug moiety. The properties of the two epimers in the prodrug moiety are not necessarily equivalent. For example, the (*S*)-epimer of the (acyloxy)alkyl ester in cefuroxime axetil **5** is hydrolyzed in animals much more rapidly than the (*R*)-epimer.[4] Oral administration of the (*R*)-epimer (acyloxy)alkyl ester **5** resulted in increased bioavailability of the parent cefuroxime versus the (*R*,*S*)-mixture. The (*R*)-epimer of cefuroxime axetil was obtained by slurrying the diastereomeric mixture of epimers in methanol followed by filtration. Additionally, preclinical candidate **7** has greater oral bioavailability than the other diastereomer **8**.[5] The two diastereomers **7** and **8** were separated by chromatography or by repeated recrystallization.

The (acyloxy)alkyl ester prodrug moiety is generally introduced by alkylation of the parent carboxylate with a haloalkyl ester. To the best of our knowledge, no methods to synthesize optically active (acyloxy)-alkyl esters have been reported in the literature. Here we report the use of the 'carboxy inversion' reaction to prepare optically active (acyloxy)alkyl esters. The carboxy inversion reaction involves the transformation of a carboxylic acid **9** and a peroxyacid **10** to an ester **11** (Scheme 2).[6] A mechanism for the reaction has been proposed on the basis of ^{18}O labeled product distribution and the stereochemical configurations of the resulting esters.[6a] In an unsymmetrical diacylperoxide **12**, the R group that better stabilizes a positive charge preferentially migrates to oxygen. Kinetic studies have determined the reaction rate follows the order: R tertiary>secondary>primary.[7] The rate of reaction is further increased if the migrating carbon in group R is attached to a heteroatom substituent (e.g. O or N).[8] Furthermore, the carboxy inversion reaction has been shown to occur predominantly with retention of configuration in several examples.[6,8,9]



1 **2** **3** **4**

Scheme 1.

Keywords: (acyloxy)alkyl ester; prodrug; carboxy inversion reaction; α-hydroxy acids; peroxyacids.

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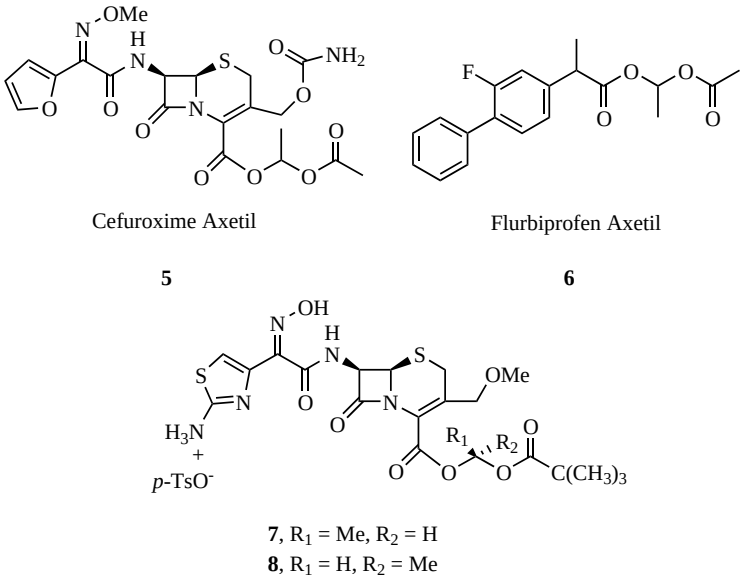
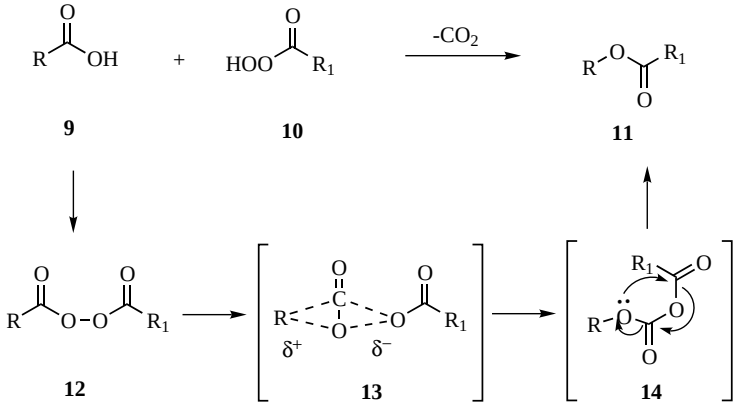


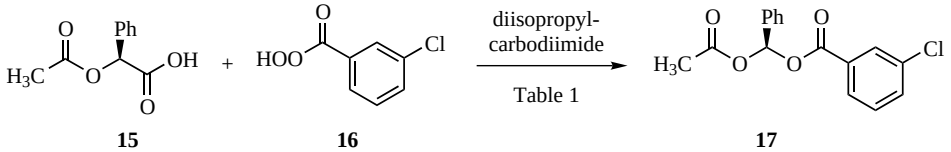
Figure 1. Structures of compounds containing a chiral (acyloxy)alkyl ester prodrug moiety.



Scheme 2.

One literature report describes the o xidative decarboxylation of carboxylic acid **15** with 3-chloroperoxybenzoic acid (**16**) through a carboxy inversion reaction to prepare (acyloxy)alkyl ester **17** (Scheme 3).[10] However, this paper did not address the question of whether this interesting transformation was stereoselective or not. We investigated this reaction further to uncover the potential utility for the preparation of optically active (acyloxy)alkyl esters and to explore applications to prodrug design. Both enantiomers of commercially available *O*-acetylmandelic acid (**15**, only *S*-isomer shown) were separately reacted with 3-chloroperoxybenzoic acid[11] (**16**) and diisopropylcarbodiimide in methylene chloride at 0°C as described in the literature.[10] The enantiomeric purity of (acyloxy)alkyl ester **17** (only *R*-isomer shown) was evaluated by chiral HPLC analysis.[12] Analysis of both *R* and *S* isomers **17** derived from the *S* and *R* isomers of **15** revealed a 2.8:1 ratio of the major enantiomer, respectively (Table 1).[13] Both enantiomers of **15** were purchased with 99% ee purity; therefore, there is significant loss of optical purity during the reaction when run according to the literature conditions. Retention of configuration was expected based on literature precedent.[6,8,9]

In an effort to enhance the enantioselectivity, we explored the effect of temperature and solvent on the reaction. The results are shown in Table 1. Lowering



Scheme 3.

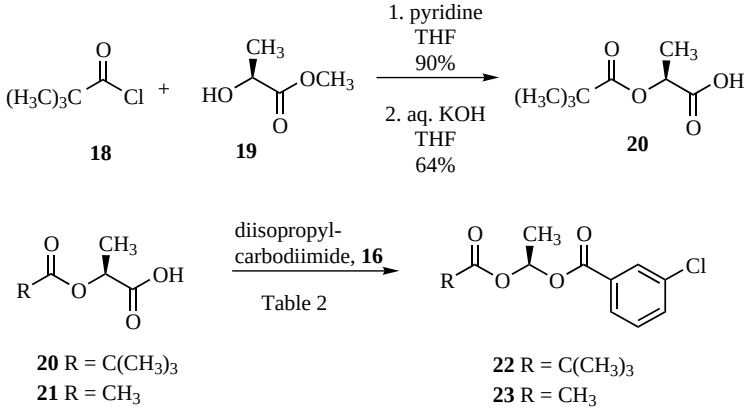
Table 1. Effect of solvent and temperature on ratio of enantiomers **17**

Entry	Solvent	Temp. (°C)	% Yield (**17**)	Ratio of enantiomers	% ee (**17**)
1	CH_2Cl_2	0	40	2.8:1	46
2	CH_2Cl_2	−40	36	3.2:1	52
3	CH_2Cl_2	−78	39	3.8:1	58
4	CH_3CN	0	15	2.2:1	36
5	THF	0	21	4.0:1	60
6	Ethyl ether	0	30	5.6:1	70
7	Isopropylether	0	20	6.0:1	71
8	Ethyl ether/hexanes 5:1	0	40	8.2:1	78
9	Toluene	0	38	8.4:1	78
10	Toluene	−40	45	9.2:1	80

the reaction temperature with methylene chloride as solvent resulted in a slight increase in enantiomeric excess (compare entries 1–3). Interestingly, the solvent has a much more dramatic effect on the enantioselectivity of the reaction. The use of acetonitrile versus methylene chloride as solvent led to a decrease in enantiomeric purity in the product (entry 4). However, the utilization of THF, ethyl ether, isopropyl ether, ethyl ether/hexanes (5:1), and toluene as solvent led to steadily increasing levels of enantioselectivity, respectively (entries 5–10). The best enantioselectivity was obtained with toluene at –40°C to give the major isomer with 80% ee (entry 10). Lower reaction temperatures using toluene as solvent were not feasible due to solubility of the reagents. The decreasing polarity of the solvent provides for better retention of stereochemical configuration of the product during the reaction. The more polar solvents may lead to increased carbocation-like intermediates, thus leading to increased loss of enantiomeric purity.

Next, we explored the carboxy inversion reaction with (*S*)-*O*-pivaloyl lactic acid (**20**) and commercially available (*S*)-*O*-acetyl lactic acid (**21**) (Scheme 4). The preparation of (*S*)-*O*-pivaloyl lactic acid (**20**) is shown and its enantiomeric purity was determined to be greater than 95% by chiral HPLC analysis. Reaction of acids **20** and **21** with 3-chloroperoxybenzoic acid (**16**) did provide (acyloxy)alkyl esters **22** and **23**. However, neither the yields nor the enantioselectivity of products **22** or **23** were as good as those observed with optically active *O*-acetyl mandelic acid (Table 2).

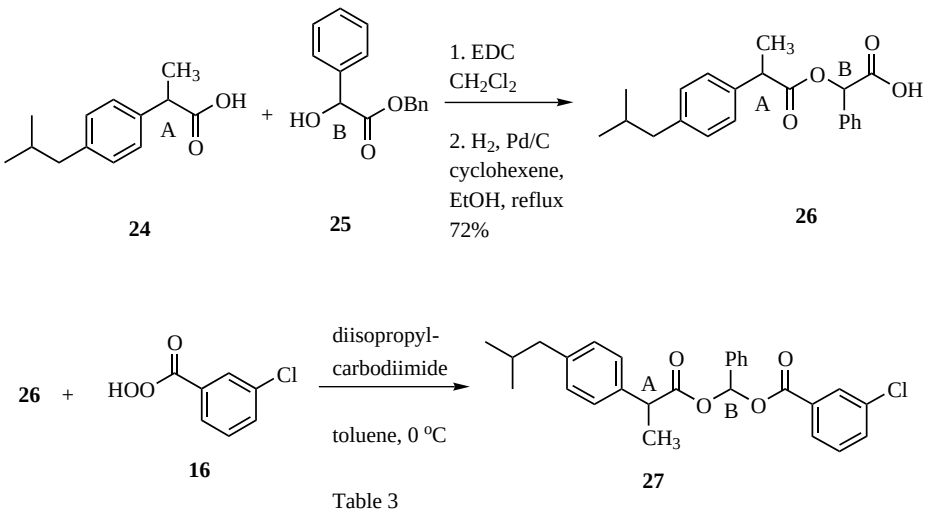
As a last set of experiments we explored the reaction with ibuprofen (**24**), a known carboxylic acid drug on the market. (Acyloxy)alkyl esters of ibuprofen are known, however, they are epimeric in the prodrug moiety.[14] Both enantiomers of ibuprofen (**24**) were independently coupled to both enantiomers of benzyl mandelate (**25**) (Scheme 5). After removal of the benzyl



Scheme 4.

Table 2. Effect of solvent and temperature on ratio of enantiomers **22** and **23**

Entry	R	Solvent	Temp. (°C)	% Yield	Ratio of enantiomers	% ee
1	$C(CH_3)_3$ (**22**)	CH_2Cl_2	0	34	3.2:1	52
2	$C(CH_3)_3$ (**22**)	CH_2Cl_2	−78	20	4.4:1	63
3	$C(CH_3)_3$ (**22**)	Toluene	0	12	3.7:1	57
4	CH_3 (**23**)	CH_2Cl_2	0	9	3.2:1	52
5	CH_3 (**23**)	Ethyl ether	0	10	3.9:1	59
6	CH_3 (**23**)	Toluene	0	9	3.2:1	52



Scheme 5.

Table 3. Stereochemistry and ratio of diastereomers for **27**

Entry	Stereochemistry of A	Stereochemistry of B	% Yield (**27**)	Ratio of diastereomers at B	% de (**27**)
1	*S*	*R*	20	25.7:1.0	92
2	*S*	*S*	33	11.2:1.0	84
3	*R*	*S*	20	21.9:1.0	91
4	*R*	*R*	33	11.6:1.0	84

ester, the corresponding acid **26** was treated with 3-chloroperoxybenzoic acid, as described before, to provide **27**. Racemization was not detected at stereocenter A. Interestingly, the diastereomeric purity at stereocenter B for all four reaction products was uniformly higher than the model systems described before (Table 3). Surprisingly, the enantiomeric pair (*SR* and *RS*) possessed higher diastereomeric purity at stereocenter B than the other enantiomeric pair (*SS* and *RR*). Presumably, some type of chiral matching is leading to increased retention of enantiomeric integrity in the reaction.

In summary, we have described methodology for the preparation of enantiomerically enriched (acyloxy)alkyl esters from *O*-acyl-α-hydroxy acids through the carboxy inversion reaction.[15] In principle, this reaction could be extended to include other optically active *O*-acyl-α-hydroxy acids and peroxyacids to prepare a variety of enantiomerically enriched (acyloxy)alkyl esters which could be of interest as prodrug moieties.

References

1. (a) Bundgaard, H. *Drugs Future* **1991**, *16*, 443; (b) Silverman, R. B. *The Organic Chemistry of Drug Design and Drug Action*; Academic Press, 1992; Chapter 8; (c) Bundgaard, H., Ed. *Design of Prodrugs*; Elsevier: Amsterdam, 1985; (d) Sinkula, A. A.; Yalkowsky, S. H. *J. Pharm. Sci.* **1975**, *64*, 181.
2. Gregson, M.; Sykes, R. B. *Ger. Offen.* 1977, DE 2706413; *Chem. Abstr. 87*, 184523.
3. Mimura, M.; Uchida, K.; Ieda, T.; Kimura, K. *Jpn. Kokai*, *Tokkyo Koho* 1989, JP 01211550; *Chem. Abstr. 112*, 98217.
4. Mosher, G. L.; Mullen, M. V. US patent 5,063,224, 1991.
5. (a) Fleischmann, K.; Adam, F.; Durckheimer, W.; Hertzsch, W.; Horlein, R.; Jendralla, H.; Lefebvre, C.; Mackiewicz, P.; Roul, J.-M.; Wollmann, T. *Liebigs Ann.* **1996**, 1735; (b) Defossa, E.; Fischer, G.; Gerlach, U.; Horlein, R.; Isert, D.; Krass, N.; Lattrell, R.; Stache, U.; Wollmann, T. *Liebigs Ann.* **1996**, 1743.
6. (a) Kashiwagi, T.; Kozuka, S.; Oae, S. *Tetrahedron* **1970**, *26*, 3619; (b) Linhardt, R. J.; Murr, B. L.; Montgomery, E.; Osby, J.; Sherbine, J. *J. Org. Chem.* **1982**, *47*, 2242.
7. Denny, D. B.; Sherman, N. *J. Org. Chem.* **1965**, *30*, 3760.
8. Shiozaki, M. *Synthesis* **1990**, 691.
9. (a) Hatanaka, M.; Ueda, I. *Chem. Lett.* **1991**, 61; (b) Shiozaki, M.; Ishida, N.; Sato, S. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 3950; (c) Akhtar, M.; Gani, D. *Tetrahedron* **1987**, *43*, 5341; (d) Marshall, J. A.; Andrews, R. C. *Tetrahedron Lett.* **1986**, *27*, 5197.
10. Shiozaki, M. *J. Org. Chem.* **1991**, *56*, 528.
11. Technical grade 3-chloroperoxybenzoic acid was purified according to a literature procedure described by Perrin, D. D.; Armaraego, W. L. F. *Purification of Laboratory Chemicals*, 3rd ed.; Butterworth-Heinemann, 1988.
12. The enantiomeric ratios were measured on an analytical Chiralpak AD column using 97:3 hexanes/isopropanol as the mobile phase with a flow rate of 1 mL/min and detection at 230 nm.
13. The change in *R* and *S* stereochemical designation for product **17** is due to changed priorities.
14. (a) Rephaeli, A. WO 98/40078; (b) Nudelman, A.; Rephaeli, A.; Neiss, E.; Loev, B. WO 98/40066.

15. **General procedure**. To (*S*)-(*O*)-acetyl mandelic acid (250 mg, 1.29 mmol) in toluene (5.5 mL) in an ice bath was added 3-chloroperoxybenzoic acid (245 mg, 1.42 mmol) followed by diisopropylcarbodiimide (225 μL, 1.42 mmol). The solution was stirred for 1 h at 0°C, water was added and then the mixture was extracted with methylene chloride (2×25 mL). The organic layer was dried over Na_2SO_4, filtered and evaporated to give 495 mg of a semi-solid. The residue was chromatographed on a wet-packed silica gel column (3×13 cm) eluting with hexanes/ethyl acetate (96:4). The appropriate fractions were combined and evaporated to give 149 mg of a clear oil (38%).

Compound 17. Clear oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.16 (s, 3H), 7.39 (t, J=7.8 Hz, 1H), 7.43 (m, 3H), 7.54 (dd, J=1.7, 7.8 Hz, 1H), 7.60 (m, 2H), 7.93 (s, 1H), 7.95 (d, J=7.9 Hz, 1H), 8.04 (t, J=1.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.8, 90.4, 126.7, 128.1, 128.7, 129.8, 129.9, 131.2, 133.6, 134.6, 135.2, 163.7, 168.7. Anal. Calcd for $C_{16}H_{13}ClO_4$: C, 63.06; H, 4.30. Found: C, 62.85; H, 4.16.

Compound 22. Clear oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.22 (s, 9H), 1.61 (d, J=5.4 Hz, 3H), 7.07 (q, J=5.4 Hz, 1H), 7.40 (t, J=7.8 Hz, 1H), 7.54 (dd, J=2.4, 6.8 Hz, 1H), 7.91 (dd, J=2.0, 6.2 Hz, 1H), 8.00 (t, J=2.0 Hz, 1H).

Compound 23. Clear oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.61 (d, J=5.3 Hz, 3H), 2.10 (s, 3H), 7.10 (q, J=5.6 Hz, 1H), 7.39 (t, J=7.9 Hz, 1H), 7.55 (dt, J=1.4, 7.2 Hz, 1H), 7.93 (dt, J=1.4, 7.9 Hz, 1H), 8.01 (t, J=1.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.9, 21.1, 89.5, 128.3, 130.1, 130.2, 131.4, 133.7, 134.9, 163.6, 169.2; R_f=0.35 (hexanes/ethyl acetate, 95:5, visualized by UV). Anal. Calcd for $C_{11}H_{11}ClO_4$: C, 54.45; H, 4.57. Found: C, 54.78; H, 4.29.

Compound 27 (*S*,*S*). Clear oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (d, J=6.6 Hz, 6H), 1.53 (d, J=7.1 Hz, 3H), 1.83 (m, 1H), 2.44 (d, J=7.2 Hz, 2H), 3.79 (q, J=7.2 Hz, 1H), 7.06 (d, J=8.1 Hz, 2H), 7.10 (d, J=8.5 Hz, 1H), 7.17 (d, J=8.1 Hz, 2H), 7.29–7.41 (m, 5H), 7.54 (ddd, J=1.1, 2.1, 8.0 Hz, 1H), 7.92 (s, 1H), 7.93 (dt, J=1.3, 7.7 Hz, 1H), 8.00 (t, J=1.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.5, 22.7, 30.6, 45.4, 77.6, 90.8, 126.9, 127.7, 128.5, 128.9, 129.8, 130.0, 130.2, 130.4, 131.4, 133.9, 135.1, 135.6, 137.3, 141.1, 163.7, 172.8. Anal. Calcd for $C_{27}H_{27}ClO_4$: C, 71.91; H, 6.03. Found: C, 72.18; H, 6.21.

Compound 27 (*S*,*R*). Clear oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (d, J=6.9 Hz, 6H), 1.51 (d, J=7.2 Hz, 3H), 1.84 (m, 1H), 2.43 (d, J=7.2 Hz, 2H), 3.79 (q, J=7.2 Hz, 1H), 7.07 (d, J=8.2 Hz, 2H), 7.19 (d, J=8.2 Hz, 2H), 7.34 (d, J=7.9 Hz, 1H), 7.39 (m, 3H), 7.51 (m, 3H), 7.79 (dt, J=7.8, 1.2 Hz, 1H), 7.89 (t, J=1.8 Hz, 1H), 7.92 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.5, 22.7, 30.5, 45.4, 77.6, 90.8, 126.8, 127.6, 128.5, 129.0, 129.8, 130.1, 130.2, 130.3, 131.3, 133.8, 134.9, 135.6, 137.3, 141.1, 163.5, 172.8.