ORGANIC LETTERS

2001
Vol. 3, No. 9
1315−1318

Enantioselective Synthesis of (−)-Roccellaric Acid

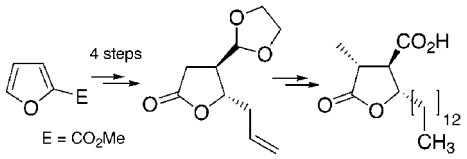
Claudius Böhm and Oliver Reiser*

Institut für Organische Chemie, Universität Regensburg, Universitätsstr. 31, 93053 Regensburg, Germany

oliver.reiser@chemie.uni-regensburg.de

Received February 9, 2001

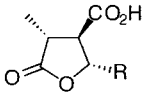
ABSTRACT



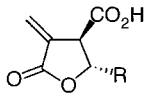
1 **(−)-13** **(−)-17**

A new strategy for the synthesis of *anti*-4,5-disubstituted γ-butyrolactones starting from inexpensive furan-2-carboxylic methyl ester was developed. By applying this methodology, the enantioselective synthesis of (−)-roccellaric acid ((−)-17) was accomplished using a copper(I)-catalyzed asymmetric cyclopropanation, a tin(IV)-catalyzed retroaldol/lactonization sequence of cyclopropanols, and a ruthenium-catalyzed intermolecular metathesis reaction as key steps.

γ-Butyrolactones can be found as important constituents in an abundant number of natural products.[1] Approaches toward the stereoselective synthesis of this structure are therefore a continuing challenge in organic synthesis.[2] Trisubstituted γ-butyrolactones,[3] such as paraconic acids (4-carboxy-substituted γ-butyrolactones) have attracted considerable interest because of their antibiotic and antitumor properties.[4]



R = n-$C_{13}H_{27}$: (−)-Roccellaric acid
R = n-$C_{11}H_{23}$: (−)-Nephrosteramic acid



R = n-$C_{13}H_{27}$: (−)-Protolichesterinic acid
R = n-C_5H_{11}: (−)-Methylenolactocin

Consequently, a number of syntheses have been developed leading to these natural products either in racemic[5] or enantiopure form using starting materials from the chiral pool,[6] chiral auxiliaries,[7] or—applying catalytic asymmetric methodology—the Sharpless epoxidation as the key step.[8] We present here a strategy for the catalytic asymmetric synthesis of *anti*-4,5-disubstituted γ-butyrolactones **2** or **3**

(1) Koch, S. S. C.; Chamberlin, A. R. *Enantiomerically Pure γ-Butyrolactones in Natural Products Synthesis*; Atta-ur-Rahman, Ed.; Elsevier Science: Amsterdam, 1995; pp 687−725.

(2) Leading reviews: Ogliaruso, M. A.; Wolfe, J. F. In *Synthesis of Lactones and Lactams*; John Wiley & Sons: New York, 1993.

(3) (a) Miyabe, H.; Fujii, K.; Goto, T.; Naito, T. *Org. Lett.* **2000**, *2*, 4071−4074. (b) Fernandez, A.-M.; Plaquevent, J.-C.; Duhamel, L. *J. Org. Chem.* **1997**, *62*, 4007−4014. (c) Sibi, M. P.; Lu, J.; Talbacka, C. L. *J. Org. Chem.* **1996**, *61*, 7848−7855. (d) Peng, Z-H.; Woerpel, K. A. *Org. Lett.* **2001**, *3*, 675−678.

(4) (a) Maier, M. S.; Marimon, D. I. G.; Stortz, C. A.; Adler, M. T. *J. Nat. Prod.* **1999**, *62*, 1565−1567. (b) Park, B. K.; Nakagawa, M.; Hirota, A.; Nakayama, M. *J. Antibiot.* **1988**, *41*, 751.

(5) Lertvorachon, J.; Meepowpan, P; Thebtaranonth, Y. *Tetrahedron* **1998**, *54*, 14341−14358. (b) Mandal, P. K.; Maiti, G.; Roy, S. C. *J. Org. Chem.* **1998**, *63*, 2829−2834. (c) Ghatak, A.; Sarkar, S.; Ghosh, S. *Tetrahedron* **1997**, *53*, 17335−17342. (d) Damon, R. E.; Schlessinger, R. H. *Tetrahedron Lett.* **1976**, 1561−1564. (e) Carlson, R. M.; Oyler, A. R. *J. Org. Chem.* **1976**, *41*, 4065−4069. (f) Martin, J.; Watts, P. C.; Johnson, F. *J. Org. Chem.* **1974**, *39*, 1676−1681. (g) Löffler, A.; Pratt, R. D.; Pucknat, J.; Gelbard, G.; Dreiding, A. S. *Chimica* **1969**, *23*, 413−416. (h) van Tamelen, E. E.; Bach, S. R. *J. Am. Chem. Soc.* **1958**, *80*, 3079−3086.

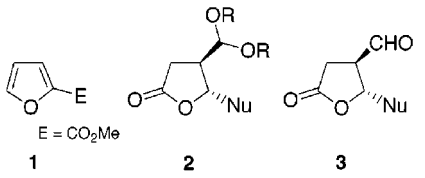
(6) (a) Masaki, Y.; Arasaki, H.; Itoh, A. *Tetrahedron Lett.* **1999**, *40*, 4829−4832. (b) Mulzer, J.; Salimi, N.; Hartl, H. *Tetrahedron: Asymmetry* **1993**, *4*, 457−471.

(7) (a) Bella, M.; Margarita, R. Orlando, C.; Orsini, M.; Parlanti, L.; Piancatelli, G. *Tetrahedron Lett.* **2000**, *41*, 561−565. (b) Sibi, M. P.; Ji, J. *Angew. Chem.* **1997**, *109*, 266−268. (c) Sibi, M. P.; Deshpande, P. K.; Loggia, A. J. L. *Synlett* **1996**, 343−345. (d) Murta, M. M.; Azevedo, M. B. M. d.; Greene, A. E. *J. Org. Chem.* **1993**, *58*, 7537−7541. (e) de Azevedo, M. B. M.; Murta, M. M.; Greene, A. E. *J. Org. Chem.* **1992**, *57*, 4567−4569.

(8) (a) Chandrasekharam, M.; Liu, R.-S. *J. Org. Chem.* **1998**, *63*, 9122−9124. (b) Martin, T.; Rodriguez, C. M.; Martin, V. S. *J. Org. Chem.* **1996**, *61*, 6450−6453. (c) Takahata, H.; Uchida, Y.; Momose, T. *J. Org. Chem.* **1995**, *60*, 5628−5633. (c) Zhu, G.; Lu, X. *J. Org. Chem.* **1995**, *60*, 1087−1089.

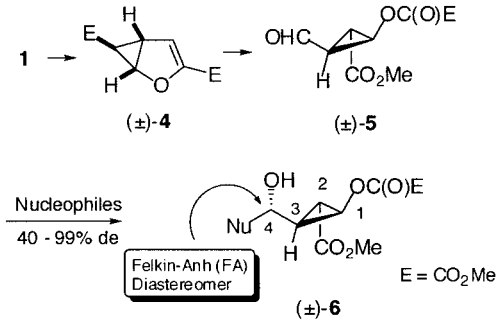
10.1021/ol015686u CCC: $20.00
Published on Web 04/04/2001

starting with an asymmetric cyclopropanation of inexpensive furan-2-carboxylic methyl ester (**1**) and making use of Sn(IV) or barium hydroxide catalyzed retroaldol/lactonization of cyclopropanols. Using this methodology, a short synthesis of (−)-**17**, the enantiomer of the natural occurring (+)-roccellaric acid, was developed.



We reported recently a diastereoselective, three-step synthesis of highly functionalized cyclopropanes (±)-**6**.[9] The key step is the copper(I)-catalyzed cyclopropanation of **1** with methyl diazoacetate,[10] which occurs regioselectively at the lesser substituted double bond and diastereoselectively, orienting the methyl ester onto the convex face of the bicyclic structure in (±)-**4**. Ozonolysis and reductive workup gives rise to (±)-**5**, which undergoes addition of nucleophiles, yielding (±)-**6** with good to excellent Felkin−Anh[11] selectivity (Scheme 1).

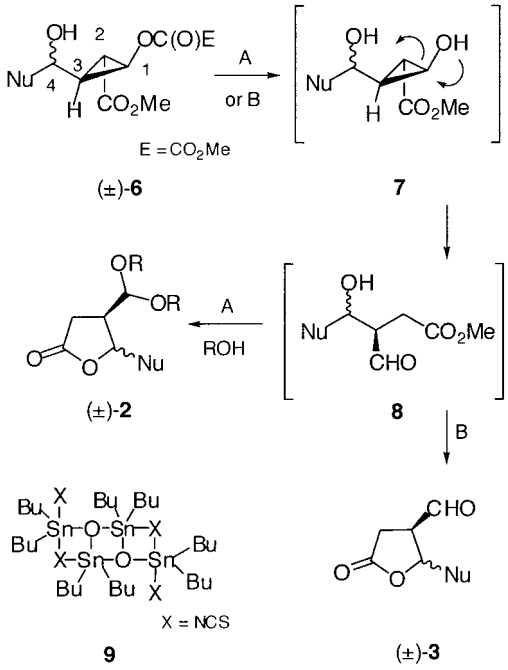
Scheme 1



The cyclopropanes (±)-**6** have several interesting characteristics that should prove useful for further synthetic transformations. The hydroxyl group at C-4, which was created by addition of the nucleophile, is located in a γ-position to the ester group at C-2 of the cyclopropane moiety. Furthermore, the vicinal donor−acceptor relationship between the hydroxy group at C-1 and the ester group at C-2 should make ring opening of the cyclopropane feasible.[12] These two features opened up the possibility to develop a retroaldol/lactonization sequence of (±)-**6** to *anti*-4,5-disubstituted γ-butyrolactones (±)-**2** or (±)-**3**, respectively.

To initiate the ring opening of the cyclopropane moiety in **6** we attempted to demask the donor properties of the acylated hydroxy group at C-1 by transesterification. Thus, using the Sn(IV) catalyst **9**[13] resulted in the smooth formation of (±)-**2**, in which saponification to **7** followed by ring opening to **8**, acetalization of the aldehyde group, and lactonization all had occurred in a single step (Scheme 2, Table 1).

Scheme 2. Retroaldol/Lactonization Sequence of **6** to (±)-**2** (Method A) and (±)-**3** (Method B), Respectively[a]



[a] Method A: **9** (0.05 mol %), ROH. Method B: $Ba(OH)_2 \cdot 8H_2O$ (1 equiv), MeOH, 0 °C. See Table 1.

Both acyclic and cyclic acetals can be obtained in the course of this sequence, depending on the alcohol used as solvent. While methanol in general gave the highest yields of (±)-**2**, the use of 1,2-ethyleneglycole to arrive at cyclic acetals is often advantageous for reasons of stability of the products. It is also noteworthy that ketones and alkenes are compatible with the reaction conditions applied and do not react with the alcohols employed as the solvents. Nevertheless, difficulties to provide clean lactone products were encountered with acid-sensitive functionalities in the substrates such as allylic alcohols or allylic acetates.

Alternatively, the ring opening of **6** can be effected by treatment with barium hydroxide to arrive at lactones (±)-**3**, having the aldehyde group available in unprotected form for further synthetic transformations. In all cases, the

(9) Böhm, C.; Schinnerl, M.; Bubert, C.; Zabel, M.; Labahn, T.; Parisini, E.; Reiser, O. *Eur. J. Org. Chem.* **2000**, 2955−2965.

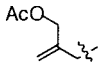
(10) The rhodium(II)-catalyzed cyclopropanation of **1** has also been reported: Wenkert, E.; Guo, M.; Lavilla, R.; Porter, B.; Ramachandran, K.; Sheu, J.-H. *J. Org. Chem.* **1990**, *55*, 6203−6214.

(11) Leading review: Mengel, A.; Reiser, O. *Chem. Rev.* **1999**, *99*, 1191−1223.

(12) Leading review: Reissig, H.-U. *Top. Curr. Chem.* **1988**, *144*, 73. Recent examples for synthetic applications of donor−acceptor substituted cyclopropanes via ring opening: (a) Pulz, R.; Watanabe, T.; Schade, W.; Reissig, H. U. *Synlett* **2000**, 983−986. (b) Ullmann, A.; Gruner, M.; Reissig, H.-U. *Chem. Eur. J.* **1999**, *5*, 187−197.

(13) (a) Otera, J.; Dan-oh, N.; Nozaki, H. *Tetrahedron* **1992**, *48*, 1449−1456. (b) Otera, J.; Dan-oh, N.; Nozaki, H. *J. Org. Chem.* **1991**, *56*, 5307−5311. (c) Okawara, R.; Wada, M. *Adv. Organomet. Chem.* **1967**, *5*, 137.

Table 1. Retroaldol/Lactonization Sequence of **6** to (±)-**2** (Method A) and (±)-**3** (Method B), Respectively

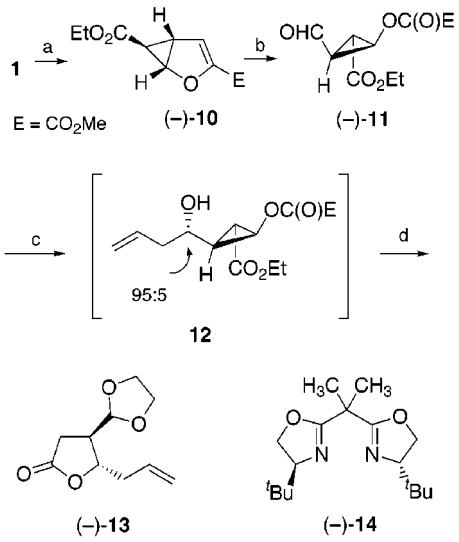
Nu	A[a] → (±)-**2** yield [%]	R	dr[b]	B[c] → (±)-**3** yield [%]
	66	CH_3	99:1	–
	26	$-(CH_2)_2-$	99:1	–
	74	CH_3	95:5	–
	72	$-(CH_2)_2-$	95:5	–
	–	n.a.[d]	95:5	80
	–	n.a.[d]	80:20	73

[a] **9** (0.05 mol %), ROH. [b] Diastereomeric ratio of **6**, **2**, and **3**, respectively. [c] $Ba(OH)_2 \cdot 8H_2O$ (1 equiv), MeOH, 0 °C. [d] Not applicable.

diastereomeric ratio of the cyclopropanes **6** (Felkin−Anh/*anti*-Felkin−Anh at C-4) and the lactones (±)-**2** and (±)-**3** (*anti/syn*) was identical, indicating that no epimerization during the retroaldol/lactonization sequences occurs.

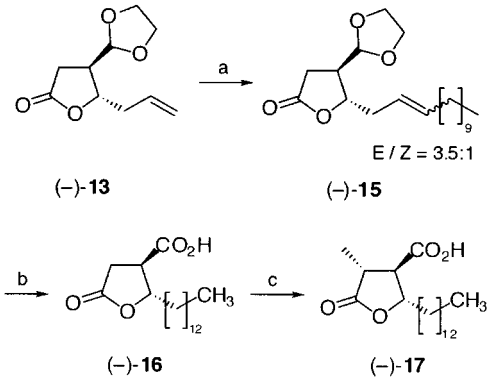
On the basis of this strategy we were able to develop a short asymmetric synthesis of (−)-roccellaric acid ((−)-**17**)

Scheme 3[a]



[a] (a) (i) ethyl diazoacetate, $Cu(OTf)_2$ (2 mol %), (−)-**14** (2.5 mol %), $PhNHNH_2$ (2 mol %), CH_2Cl_2, 91% ee; (ii) recrystallization (pentane), >99% ee, 53%. (b) (i) O_3, CH_2Cl_2, −78 °C; (ii) dimethyl sulfide, 94%. (c) (i) $BF_3 \cdot OEt_2$, −78 °C; (ii) allyltrimethylsilane. (d) **9** (0.05 mol %), 1,2-ethyleneglycol, benzene, reflux, *anti/syn* 95:5, 72% (two steps).

Scheme 4[a]



[a] (a) 1-dodecene (1.5 equiv), $(PCy_3)_2RuCl_2(=CHPh)$ (5 mol %), 64%. (b) (i) H_2 (1 bar), Pd/C (5 mol %); (ii) CrO_3, H_2SO_4; (iii) recrystallization ethyl acetate, 85%. (c) NaHMDS (2.2 equiv), MeI (9.6 equiv), 96%.

(Schemes 3 and 4). The cyclopropanation of **1** could be rendered asymmetric by using the bisoxazoline (−)-**14**[14] as a chiral ligand; on a 40 mmol scale (−)-**10** was obtained with 91% ee, which could be raised to enantiopurity by a single recrystallization from pentane (total yield 53%).[15] It proved to be essential to use instead of methyl diazoacetate the corresponding ethyl ester, which improved the enantioselectivity of this transformation and, more important, yielded a crystalline derivative.

Ozonolysis followed by reductive work up gave rise to (−)-**11** in diastereo- and enantiomerically pure form. Boron trifluoride mediated addition of allyltrimethylsilane yielded **12** as a 95:5 diastereomeric mixture, which was, without prior isolation, directly transformed upon catalysis with **9** to the lactone (−)-**13** (72% yield, 95:5 *anti/syn*). The minor *syn*-diastereomer can be readily separated by chromatography; however, for the synthesis of (−)-roccellaric acid ((−)-**17**) it proved to be more convenient to remove it by recrystallization at a later stage (vide infra).

Lactone (−)-**13** can be envisioned as an ideal precursor to various paraconic acids. To arrive at (−)-roccellaric acid ((−)-**17**) the required tridecyl side chain was introduced by a cross-metathesis reaction[16] with 1-dodecene using the Grubbs catalyst.[17] When 1.5 equiv of this alkene was employed, no homocoupling of (−)-**13** was observed; the only byproduct formed was the homocoupling product of 1-dodecene, which is readily removed by chromatography. This way, (−)-**15** was obtained in 64% yield as a 3.5:1 mixture of *E/Z*-isomers. The latter was of no consequence

(14) (a) Evans, D.; Peterson, G. S.; Johnson, J. S.; Barnes, D. M.; Campos, K. R.; Woerpel, K. A. *J. Org. Chem.* **1998**, *63*, 4541−44. (b) Evans, D. A.; Woerpel, K. A.; Hinman, M. M.; Faul, M. M. *J. Am. Chem. Soc.* **1991**, *113*, 726−728.

(15) Using (−)-**14** constitutes a considerable improvement in yield as to our previously published procedure (ref 9).

(16) (a) Randl, S.; Gessler, S.; Wakamatsu, H.; Blechert, S. *Synlett* **2001**, 430−32. (b) Chatterjee, A. K.; Morgan, J. P.; Scholl, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 3783−84. (c) Brümmer, O.; Rückert, A.; Blechert, S. *Chem. Eur. J.* **1997**, *3*, 441−446.

(17) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18−29.

since in the next step the double bond was hydrogenated in quantitative yield using hydrogen and palladium on charcoal. Subsequently, deprotection of the acetal function and oxidation was achieved in a single transformation using Jones reagent. After recrystallization to remove the minute amount of the *syn*-epimer still present, the carboxylic acid (−)-**16** was obtained as a single stereoisomer in 85% yield.

The methylation of (−)-**16** was already described in the literature to proceed in 55% yield.[7c] Following a protocol used in the synthesis of phaseolinic acid,[18] we were able to improve this final step to give rise to (−)-roccellaric acid ((−)-**17**) in 96% yield. Furthermore, (−)-**16** has also served as a key intermediate for the synthesis of (−)-protolichesterinic aicd.[7d]

(18) Drioli, S.; Felluga, F.; Forzato, C.; Nitti, P.; Pitacco, G.; Valentin, E. *J. Org. Chem.* **1998**, *63*, 2385−2388.

In conclusion, we have developed a new asymmetric strategy to 4,5-*anti*-disubstituted γ-butyrolactones. Their application as precursors to paraconic acids was demonstrated with the synthesis of roccellaric acid.

Acknowledgment. This work was supported by the Fonds der Chemischen Industrie and by Degussa AG. We thank Ms. Doris Kaufmann for technical assistance.

Supporting Information Available: Detailed experimental procedures and analytical data for all new compounds; copies of ^{1}H and ^{13}C NMR spectra of **2**, **3**, **11**−**13**, **15**−**17**; and X-ray structure analysis of **16**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL015686U