Tetrahedron: *Asymmetry* 21 (2010) 771–773

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

Enantioselective synthesis of (*S*)-homocitric acid lactone and (*R*)-per-homocitric acid lactone involving organocatalysis

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ARTICLE INFO

Article history:
Received 19 April 2010
Accepted 23 April 2010
Available online 2 June 2010

ABSTRACT

A concise enantioselective synthesis of (*S*)-homocitric acid lactone and its homolog, via an organocatalytic vinylogous Mukaiyama–Michael reaction of a silyloxy furan derivative and acrolein, is described.

1. Introduction

(*R*)-Homocitric acid **1** (Fig. 1) is a key intermediate in the biosynthesis of L-lysine, an essential amino acid in some yeast and fungi,[1] and it is also a component of the Fe–Mo cofactor in nitrogenase.[2] The unique biological profile of homocitric acid is of interest in the development of antifungal therapies[3] and in the elucidation of the details of nitrogen fixation.[4] Studies toward these objectives require access to enantiomerically enriched (*R*)-homocitric acid and its analogs,[5] neither of which are commercially available in significant amounts. Consequently, the enantioselective synthesis of homocitric acid, invariably isolated as its γ-lactone, has been actively investigated in recent years.[6] Syntheses of racemic homocitrate[7] and per-homocitrate[7a] have also been reported. Close congeners of homocitrate such as the alkyl citrate, isocitrate, and α-alkyl malate motifs are key pharmacophoric units in several bioactive alkaloids, glycosides, and antifungal agents.[8] This has added to the interest in substituted α-hydroxy di- and tricarboxylic acid derivatives in recent years. Herein, we report an expeditious synthesis of (*S*)-homocitric acid lactone **2** as well as its homolog, (*R*)-per-homocitric acid lactone **3**.

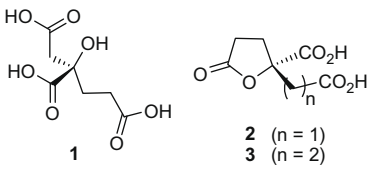

Figure 1. (*R*)-Homocitric acid **1**, (*S*)-homocitric acid lactone **2**, and (*R*)-per-homocitric acid lactone **3**.

2. Results and discussion

Our approach to homocitric acid lactone is based on the Mukaiyama–Michael reaction[9] of silyloxy furans and α,β-unsaturated aldehydes and ketones, which is a useful method for the construction of butenolides. The iminium ion-catalyzed version of this reaction was pioneered by MacMillan[10a,b] and other organocatalytic variants have since been developed.[10e–g] We reasoned that the use of acrolein as the Michael acceptor in a conjugate addition reaction with an appropriately substituted furan would lead directly to the homocitrate lactone motif (Fig. 2).

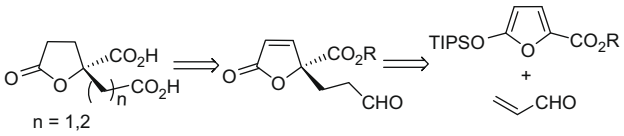

Figure 2. Vinylogous Mukaiyama–Michael approach to homocitrates.

With this objective in mind, the furans **4**[11a] and **5** were readily prepared from crotonolactone by adapting the literature procedure.[11b] Amines **6**–**9** were chosen as potential catalysts for the organocatalytic conjugate addition reaction of **4** and **5** with acrolein. Orienting experiments were conducted with furan **4** and acrolein in the presence of the MacMillan first generation catalyst **6** (Table 1). Although the required product was not obtained in ethereal solvents, the use of halogenated solvents was beneficial and **10** was obtained in modest yield and in 73% ee in chloroform, with water as an additive (Table 1, entry 5). The enantioselectivity with the MacMillan catalyst **7** was low. Interestingly, a change in the ester alkyl group had a beneficial effect on enantioselection. Thus, the use of furan **5**[12] (benzyl ester) as the nucleophile in $CHCl_3/H_2O$ provided the Michael adduct **11**[12] in 80% ee and 38% yield. Increasing the amount of acrolein (20 equiv, entry 9) was not beneficial and provided only 19% of **11** with significantly lower enantiomeric

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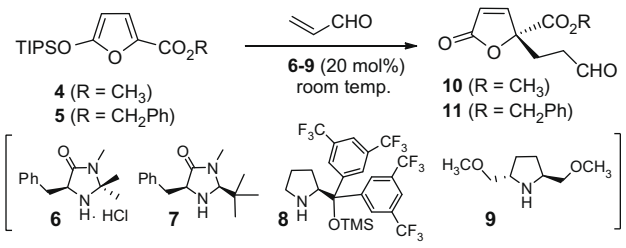
doi:10.1016/j.tetasy.2010.04.050

Table 1



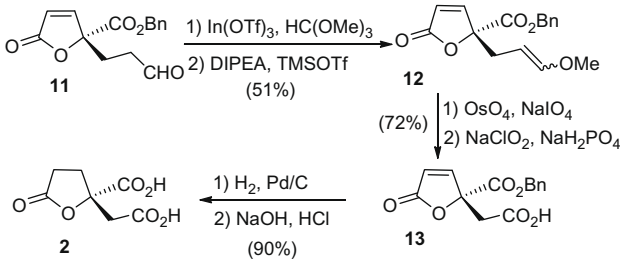
Entry	Cat.	Solvent	Add.	Time (h)	Yield (%)		ee[a] (%)
					10	**11**	
1	6	THF	H_2O[b]	16	—		—
2	6	Dioxane	H_2O	16	—		—
3	6	CH_2Cl_2	H_2O	156	18		52
4	6	$CHCl_3$	H_2O	156	12		45
5	**6**	**$CHCl_3$**	**H_2O**	**72**	**24**		**73**
6	7	THF	TFA[c]	72	21		13
7	7	CH_2Cl_2	TFA	3[d]	9		20
8	**6**	**$CHCl_3$**	**H_2O**	**72**		**38**	**80**
9	6	$CHCl_3$	H_2O	20		19[e,f]	69
10	6	THF	H_2O	20		16	1
11	7	$CHCl_3$	H_2O	144		—	—
12	7	$CHCl_3$	TFA	48		33[e]	39
13	7	$CHCl_3$	TFA	72[f]		47	72
14	7	THF	TFA	50		50	59
15	7	CH_2Cl_2	TFA	48[f]		41	41
16	8	$CHCl_3$	H_2O	120		36	50
17	8	THF	—	91		74	35
18	8	CH_2Cl_2	—	120		33	44
19	9	$CHCl_3$	H_2O	168		27	1
20	9	$CHCl_3$	MeOH	192		35	3

[a] Chiral HPLC analysis of **11** and of the acetal with (2*R*,3*R*) butanediol for **10**.
[b] 2 equiv water.
[c] 0.2 equiv TFA.
[d] Reaction at −40 °C.
[e] 20 equiv acrolein.
[f] Reaction at 0 °C.

excess (69% ee). As with **4**, changing the solvent to THF was detrimental (1% ee). This observation suggests that the reaction is sensitive to changes in the solvent. Ethereal solvents, in particular, are detrimental to enantioselection. Reactions of **5** in the presence of amines **7**–**9** also provided the butenolide **11** (Table 1, entries 10–18). When **7** was used under the conditions optimized for **6** ($CHCl_3/H_2O$ as the solvent) **11** was not obtained. The use of TFA as an additive (instead of water) had a pronounced effect and **11** was obtained, but with low ee (39%, entry 12). In summary, the best conditions for the synthesis of **11** employ the ester **5** with an excess (3 equiv) of acrolein and catalyst **6** in $CHCl_3/H_2O$ as the solvent.

Among the remaining catalysts, the imidazolidinone **7** was superior. Reactions with the prolinol derivative **8** were found to be very capricious in terms of enantioselectivity, and the C_2-symmetric pyrrolidine **9** was not especially effective as a catalyst. Overall, the higher efficiency of **6** over **7** is notable in this study. It may be noted that the facial selectivity for the reaction of **4** with β-substituted acroleins is known to depend on the nature of the β-substituent and this substituent is often necessary for good stereoselectivity.[10a,d] Since these studies[10a] were conducted with catalyst **7**, an unambiguous stereochemical assignment for adducts **10** and **11** was not possible by analogy to the reported results. However, subsequent reactions of **11** were useful in determining the sense of asymmetric induction in the Mukaiyama–Michael reaction.

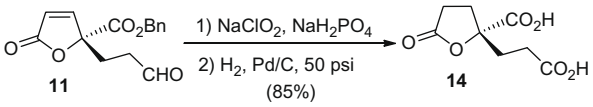
With the ester **11** (80% ee) in hand, we proceeded to convert it into the target homocitric acid lactone via a dehomologation/oxidation protocol (Scheme 1). Acetalization of **11** with trimethylorthoformate followed by treatment of the crude acetal with Hunig's base provided the enol ether **12**[12] as a mixture of stereoisomers (*trans*/*cis* = 2/1).[13] Oxidative cleavage of the enol ether (OsO_4/$NaIO_4$) provided the acid **13**.[12] Hydrogenation of **13** was anticipated to proceed with concomitant debenzylation. However, the benzyl ester in **13** was resistant to hydrogenolysis (Pd/C, 2 atm. H_2) which invariably led to mixtures containing a trace of **2** and the dihydro analog of **13**. Nonetheless, selective reduction of the double bond in **13** was possible (1 atm. H_2), which was followed by base hydrolysis of the ester and subsequent acidification to provide (*S*)-homocitric acid lactone **2** (90% from **13**, Scheme 1).



Scheme 1.

The lactone **2** obtained in this study is dextrorotatory and is therefore assigned the (*S*) configuration ($[\alpha]_D^{23} = +30$ (*c* 1, H_2O); lit.[6c] $[\alpha]_D^{23} = -48.9$ (*c* 0.38, H_2O) for the (*R*) enantiomer). This assignment also establishes the sense of asymmetric induction in the organocatalytic Michael addition reaction leading to **11**.[14]

Given the recent interest in the higher homolog of homocitric acid (per-homocitric acid[5d,6a]), we converted lactone **11** to a homolog of **2**. Thus, oxidation of aldehyde **11** provided the corresponding acid which was hydrogenated to provide the target (*R*)-per-homocitric acid lactone **14**[12] in good yield (85%, Scheme 2). It may be noted that **14** is a desymmetrized derivative of the parent achiral triacid.



Scheme 2.

3. Conclusion

In conclusion, expedient, organocatalysis-based, enantioselective syntheses of (*S*)-homocitric acid lactone and its homolog have been developed. Notably, the methodology also provides several butenolide intermediates that offer opportunities for chemoselective functionalization. Such reactions may find applications in the synthesis of functionalized oxygen and nitrogen heterocycles. Current efforts focus on these as well as other applications of the intermediates.[15]

Acknowledgments

These investigations were supported by the Natural Sciences and Engineering Research Council of Canada and the Canada Foundation for Innovation.

References

1. Zabrieski, T. M.; Jackson, M. D. *Nat. Prod. Rep.* **2000**, *17*, 85.
2. Hoover, T. R.; Imperial, J.; Ludden, P. W.; Shah, V. K. *Biochemistry* **1989**, *28*, 2768.

3. Tanzer, M.; Shuster, J.; Harner, L.; Adachi, K.; Dezwaan, T.; Lo, S.-C.; Montenegro-Chamorro, M. V.; Frank, S.; Deveraux, B.; Mahanty, S.; Heiniger, R.; Skalchunes, A.; Pan, H.; Tarpey, R. *PCT Int. Appl.* **2003**, WO 2003046130.
4. Recent reports: (a) Durrant, M. C.; Francis, A.; Lowe, D. J.; Newton, W. E.; Fisher, K. *Biochem. J.* **2006**, *397*, 261; (b) Cao, Z.; Jin, X.; Zhou, Z.; Zhang, Q. *Int. J. Quantum Chem.* **2006**, *106*, 2161; (c) Palmer, J. G.; Doemeny, P. A.; Schrauzer, G. N. *Z. Naturforsch., B: Chem. Sci.* **2001**, *56*, 386.
5. (a) Tavassoli, A.; Duffy, J. E. S.; Young, D. W. *Org. Biomol. Chem.* **2006**, *4*, 569; (b) Madden, M. S.; Paustian, T. D.; Ludden, P. W.; Shah, V. K. *J. Bacteriol.* **1991**, *173*, 5403; (c) Molines, H.; Massoudi, M. H.; Cantacuzene, D.; Wakselman, C. *Synthesis* **1983**, 322; (d) Chen, H.-B.; Chen, L.-Y.; Huang, P.-Q.; Zhang, H.-K.; Zhou, Z.-H.; Tsai, K.-R. *Tetrahedron* **2007**, *63*, 2148; (e) Prokop, M.; Milewska, M. J. *Pol. J. Chem.* **2009**, *83*, 1317.
6. (a) Huang, P.-Q.; Li, Z.-Y. *Tetrahedron: Asymmetry* **2005**, *16*, 3367; (b) Xu, P.-F.; Matsumoto, T.; Ohki, Y.; Tatsumi, K. *Tetrahedron Lett.* **2005**, *46*, 3815; (c) Paju, A.; Kanger, T.; Pehk, T.; Eek, M.; Lopp, M. *Tetrahedron* **2004**, *60*, 9081; (d) Ma, G.; Palmer, D. R. J. *Tetrahedron Lett.* **2000**, *41*, 9209; (e) Ancliff, R. A.; Russell, A. T.; Sanderson, A. J. *Tetrahedron: Asymmetry* **1997**, *8*, 3379; (f) Gaston, H.; Rodriguez, R.; Biellmann, J.-F. *J. Org. Chem.* **1996**, *61*, 1822; for a synthesis from (−)-quinic acid, see: (g) Thomas, U.; Kalyanpur, M. G.; Stevens, C. M. *Biochemistry* **1966**, *5*, 2513.
7. (a) Li, Z.-C.; Xu, J.-Q. *Molecules* **1998**, *3*, 31; (b) Ref. 5d.
8. (a) El Bialy, S. A. A.; Braun, H.; Tietze, L. F. *Eur. J. Org. Chem.* **2005**, 2965; (b) Singh, S. B.; Link, D. L.; Doss, G. A.; Polishook, J. D.; Ruby, C.; Register, E.; Kelly, T. M.; Bonfiglio, C.; Williamson, J. M.; Kelly, R. *Org. Lett.* **2004**, *6*, 337.
9. Gorobets, E. V.; Miftakhov, M. S.; Valeev, F. A. *Russ. Chem. Rev.* **2000**, *69*, 1001.
10. (a) Brown, S. P.; Goodwin, N. C.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *125*, 1192; (b) Broths, C. J.; Carrera, D. E.; MacMillan, D. W. C. *Tetrahedron* **2009**, *65*, 6746; (c) Wang, W.; Li, H.; Wang, J. *Org. Lett.* **2005**, *7*, 1637; (d) Robichaud, J.; Tremblay, F. *Org. Lett.* **2006**, *8*, 597; (e) Takahashi, A.; Yanai, H.; Zhang, M.; Sonoda, T.; Mishima, M.; Taguchi, T. *J. Org. Chem.* **2010**, *75*, 1259; (f) Sartori, A.; Curti, C.; Battistini, L.; Burreddu, P.; Rassu, G.; Pelosi, G.; Casiraghi, G.; Zanardi, F. *Tetrahedron* **2008**, *64*, 11697; (g) Takahashi, A.; Yanai, H.; Taguchi, T. *Chem. Commun.* **2008**, 2385.
11. (a) Martin, S. F.; Barr, K. J.; Smith, D. W.; Bur, S. K. *J. Am. Chem. Soc.* **1999**, *121*, 6990; (b) Naito, S.; Escobar, M.; Kym, P. M.; Liras, S.; Martin, S. F. *J. Org. Chem.* **2002**, *67*, 4200.
12. All new compounds were fully characterized and exhibited satisfactory spectroscopic data.
13. Gassman, P. G.; Burns, S. J.; Pfister, K. B. *J. Org. Chem.* **1988**, *53*, 5576.
14. For cycloadditions of acrolein-derived iminium ions, see: (a) Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2001**, *122*, 4243; (b) Jen, W. S.; Wiener, J. J. M.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2001**, *122*, 9874.
15. (a) Butenolide-based glutamate analogs: Cohen, J. L.; Chamberlin, A. R. *Abstracts of Papers, MEDI-290, 227th ACS National Meeting*, 2004; (b) Dermatological applications of homocitric acid esters: Yu, R. J.; Van Scott, E. J. US 20070093551.