Tetrahedron Letters, Vol. 34, No. 13, pp. 2083-2086, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

Asymmetric Synthesis of γ-Hydroxy α,β-Unsaturated Amides via an AD-elimination Process; Synthesis of (+)-Coriolic Acid

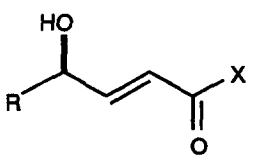
Youssef L. Bennani and K. Barry Sharpless*

Department of Chemistry, The Scripps Research Institute, 10666 N. Torrey Pines Road, La Jolla, CA 92037, U.S.A.

Abstract: *An efficient, asymmetric synthetic route to γ-hydroxy α,β-unsaturated ketone and/or aldehyde equivalents is described. Thus, 3,4-dihydroxy N-methoxy-N-methyl amides are treated in a one pot process with thionyl chloride followed by DBU to give the corresponding γ-hydroxy α,β-unsaturated amides in good yields. Based on this methodology, a short sequence leading to natural (+)-Coriolic acid is presented.*

γ-Hydroxy α,β-unsaturated carbonyl compounds of high enantiomeric purity are important compounds in organic synthesis, (Figure). The chiral allylic hydroxymethine fragment can exert a powerful stereodirecting influence in a variety of transformations such as S_N2, S_N2', 1,4-addition reactions and tin-mediated radical cyclizations.[1] Methods for the synthesis of γ-hydroxy α,β-unsaturated esters or amides include the reaction of an α-hydroxy aldehyde with olefination reagents,[2] the use of a photo-induced rearrangement of α,β-epoxy diazomethyl ketones[3] and the reaction of methyl sulfinylacetates with aldehydes followed by enzymatic kinetic resolution.[4] A related sequence to the latter has been applied to the preparation of γ-hydroxy α,β-unsaturated sulfones.[5]

Figure

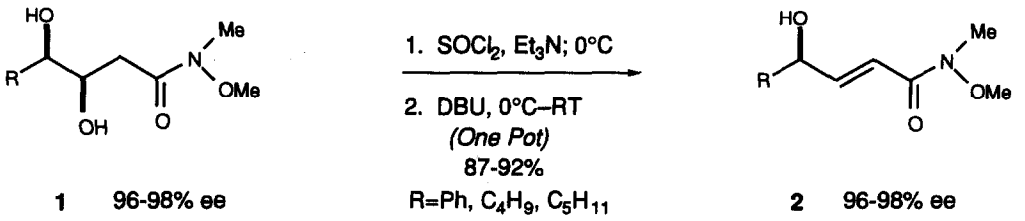


X=H; Alkyl; OR; NR_2; N-(Me)OMe

In view of the synthetic potential of this class of carbonyl compounds, it is desirable to produce them efficiently and with high enantiomeric purity. The preceding communication showed that catalytic asymmetric dihydroxylation (AD) of *trans*-disubstituted β,γ-unsaturated *N*-methoxy-*N*-methylamides[6] affords the corresponding 3,4-diols in good yields and high

enantiomeric purity.[7] As an extention of this work, we have found that when 3,4-diols of type **1** are treated, *in a one pot sequence,* with thionyl chloride in the presence of Et_3N, followed by DBU,[8] they afford in high yields the corresponding γ-hydroxy *E*-α,β-unsaturated amides **2**, (Scheme I).

Scheme I



1 96-98% ee

2 96-98% ee

The *E*-allylic alcohols of type **2** were obtained through this sequential AD-elimination method in excellent yields (87-92%) and without any detectable racemization. The combination of functionalities found in these chiral γ-hydroxy *E*-α,β-unsaturated aldehyde and ketone equivalents[9] coincides with those found in a variety of compounds in the leukotriene family as well as in many natural products and important drug intermediates.[10]

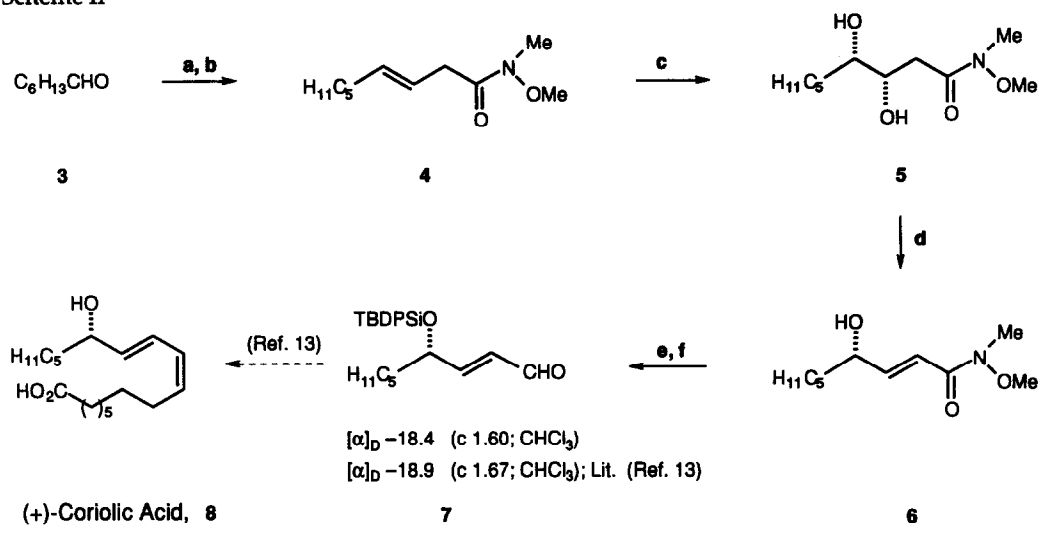
This new methodology was used to achieve a formal synthesis of natural (+)-coriolic acid (**8**), a self-defense substance against rice blast disease,[11] and an inhibitor of platelet adhesion in human endothelium cell cultures.[12] Reported syntheses of (+)-coriolic acid have relied on resolution,[13] on sugar degradation chemistry[14] or on the AE-kinetic resolution of allylic alcohols.[15]

Our synthesis starts from *n*-heptaldehyde (**3**) which was converted to the *E*-α,β-unsaturated acid (E:Z 97:3) in one step using modified Knovenagel condensation conditions[16] in 61% yield, (Scheme II). A one pot conversion of this acid to the corresponding *N*-methoxy-*N*-methylamide (**4**) (92%) followed by AD (Modified-AD-mix-α™)[17] afforded the (*3S, 4S*)-dihydroxy amide (**5**) in 83% yield and 94% ee. Treatment of a solution of diol (**5**) in dichloromethane at 0°C with thionyl chloride in the presence of triethylamine followed by DBU gave allylic alcohol (**6**) in 90% yield and 94% ee. Protection of the hydroxyl group as its *tert*-butyldiphenylsilyl ether (94%) followed by DIBAL-H reduction in tetrahydrofuran gave in excellent yield the α,β-unsaturated aldehyde (**7**) which is consistent with the reported data.[13] Aldehyde (**7**) is two synthetic steps away from the natural product according to reported literature .[12-15]

Acknowledgments

This work was supported by a grant from The National Institutes of Health (GM-28384)

Scheme II



3 4 5

(a) Malonic acid , cat. Piperidine, Xylenes, 61% (b) i. $(COCl)_2$, CH_2Cl_2, cat. DMF , 0°C-R.T. ii. MeO(Me)NH·HCl, CH_2Cl_2, Pyr (92%) (c) Modified-AD-mix- α™, $CH_3SO_2NH_2$, *t*-BuOH-H_2O; 0°C, (83%), 94% ee (d) i. $SOCl_2$, Et_3N, CH_2Cl_2, 0°C, ii. DBU, 0°C-RT, (90%) (e) TBDPSiCl, Imid., CH_2Cl_2, cat. DMF (94%); (f) DIBAL-H, -78°C-0°C, THF (92%)

References

1. (a) Craig, D.; Reader, J.C. *Tetrahedron Lett.* **1992**, *33*, 4073. (b) Arai, M.; Nemoto, T.; Ohashi, Y.; Nakamura, I. *Synlett*, **1992**, 309. (c) Hanessian, S.; Sumi, K. *Synthesis* **1991**, 1083; Hanessian, S.; Di Fabio R,; Marcoux, J.-F.; Prud'homme, M. *J. Org. Chem.* **1990**, *55*, 3436. (d) Roush, W.R.; Michaelides, M.R.; Tai, D.F.; Lesur, B.M; Chong W.K.M.; Harris, D.J. *J. Am. Chem. Soc.* **1989**, *111*, 2984. (e) Tsuda, T.; Horii, Y.; Nakagawa, Y.; Ishida, T.; Saegusa, T. *J. Org. Chem.* **1989**, *54*, 977. (f) Ziegler, F. E.; Gilligan P.J. *J. Org. Chem.* **1981**, *46*, 3874. (g) Roush, W. R.; Lesur, B.M; *Tetrahedron Lett.* **1983**, *23*, 2231. (h) Nemoto, H.; Ando, M.; Fukumoto, K. *Tetrahedron Lett.* **1990**, *31*, 6205. (i) Reetz, M. T.; Röhrig D. *Angew. Chem.* **1989**, *101*, 1732. (j) Labelle, M.; Guindon, Y. *J. Am. Chem. Soc.* **1989**, *111*, 2204. (k) Ibuka, T.; Habashita, H.; Otaka, A.; Fujii, N. *J. Org. Chem.* **1991**, *56*, 4370.

2. (a) Maryanoff, B.E.; Reitz, A.B. *Chem. Rev.* **1989**, *89*, 863. (f) Nuzillard, J.-M.; Boumendjel, A.; Massiot, G. *Tetrahedron Lett.* **1989**, *30*, 3779. (g) Netz, D.F.; Seidel, J. L. *ibid.* **1992**, *33*, 1957.

3. Waanders, P. P.; Thijs, L.; Zwanenburg, B. *Tetrahedron Lett.* **1987**, *28*,2409.

4. Burgess, K.; Cassidy, J.; Henderson, I. *J. Org. Chem.* **1991**, *56*, 2050.

5. (a) Carretero, J. C.; Dominguez, E. *J. Org. Chem.* **1992**, *57*, 3867. (b) Dominguez, E., Carretero, J. C. Fernandez-Mavoralas, A.; Conde, S. *Tetrahedron Lett.* **1991**, *32*, 5159.

6. (a) Nahm, S.; Weinreb, S.M. *Tetrahedron Lett.*, **1981**, *22*, 3815. (b) For the preparation of β,γ-unsaturated acids or amides see Ref. (9) in the preceding paper

7. (a) Bennani, Y. L.; Sharpless, K. B. *Preceding paper.* (b) Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G.A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* **1992**, *57*, 2768. (c) Amberg, W.; Bennani, Y.L.; Crispino, G.A.; Chadha, R. K.; Davis, W.; Hartung, J.; Jeong, K.-S.; Ogino; Y.; Shibata, T.; Sharpless, K.B. *J. Org. Chem. in press*).

8. Recently, a similar type of elimination giving γ-hydroxy α,β-unsaturated nitriles and sulfones were reported, Kang, S.-K.; Lee, D.-H.; Kim, Y.-S.; Kang, S.-C. *Synth. Commun.* **1992**, *22*, 1109; Kang, S.-K., Park Y. W., Kim, S. G.; Jeon, J. H. *J. Chem. Soc. Perkin Trans. 1*, **1992**, 405

9. *Typical procedure for the conversion of Amide 1 to allylic alcohol 2 (R= Ph): Under a nitrogen atmosphere, amide 1 (R=Ph, 98% ee) 280 mg (1.17 mmol) was dissolved in 10 mL of CH_2Cl_2, cooled to 0°C and 380 μL(2.70 mmol) of Et_3N was introduced. Thionyl chloride, (100 μL, 1.34 mmol) was then slowly added over a 10 min. period. The mixture was stirred at 0°C for 30 min and followed by TLC [EtOAc:Hexane 3:1; Diol: R_f=0.2; diastereomeric cyclic sulfites R_f=0.75 (2 spots)]. The mixture was warmed to RT and evaporated to dryness. The residue was dried under high vacuum (0.5 mmHg) for 1 hour then dissolved in 10 mL of CH_2Cl_2 and cooled to 0°C. DBU, (203 μL, 1.34 mmol) was slowly added and the mixture stirred at 0°C for 10 min. then at RT for 30 min. The reaction was monitored by TLC to completion [EtOAc:hexane 3:1; allylic alcohol Rf=0.4). CH_2Cl_2, 20 mL was added and the mixture washed with 10% HCl, 2x5 mL; water, 5 mL and brine, 5 mL. The organic layer was dried ($MgSO_4$) and evaporated. The product was purified by silica gel flash chromatography to give 232 mg of pure alcohol, 90% yield.*

10. (a) Corey, E.J.; Cheng, X.-M. in *"The Logic of Chemical Synthesis"* John Wiley and Sons, N.Y., **1989**, pp. 249-354 and references cited therein. (b) Nicolaou, K. C.; Webber, S. E. *Synthesis*, **1986**, 453. (c) Niwa, H.; Wakamatsu, K.; Yamada, K. *Tetrahedron Lett.* **1989**, *30*, 4543.

11. Kato, T.; Yamagushi, Y.; Hirano, T.; Yokoyama, T.; Uyehara, T.; Namai, T.; Yamanaka, S.; Harada, N. *Chem. Lett.*, **1984**, 409.

12. Setty, B.N.Y.; Berger, M.; Stuart, M.J. *Biochem. Biophys. Res. Commun.* **1987**, *148*, 528.

13. de Montarby, L.; Mosset, P.; Grée, R. *Tetrahedron Lett.* **1988**, *29*, 3937.

14. (a) Moustakis, C.A.; Weerasinghe, D.K.; Mosset, P.; Falck, J.R.; Miskowski, C. *Tetrahedron Lett.* **1986**, *27*, 303. (b) Tranchepain, I.; Le Berre, F.; Duréault, A.; Le Merrer, Y.; Depezay, J. C. *Tetrahedron*, **1989**, *45*, 2057.

15. (a) Yadav, J.S.; Deshpande, P.K.; Sharma, G.V.M. *Tetrahedron*, **1992**, *48*, 4465. For other syntheses of (+)-Coriolic acid and derivatives see (b) Chan, C.; Box, P.B.; Roberts, S.M. *J. Chem. Soc. Chem. Commun.* **1988**, 971. (c) Kobayashi, Y.; Okamoto, S.; Shimazaki, T.; Oshiai, Y.; Sato, F. *Tetrahedron Lett.* **1987**, *28*, 3959.

16. Ragoussis, N. *Tetrahedron Lett.*, **1987**, *28*, 93. In our synthesis, piperidine instead of piperidine acetate was used as the catalyst, perhaps causing a slightly lower yield than that reported.

17. In this synthesis the ligand $(DHQ)_2$-PHAL was used in a Modified-AD-mix-α™, see Ref (7a).

(Received in USA 4 January 1993; accepted 22 January 1993)