ORGANIC LETTERS

2007
Vol. 9, No. 22
4651−4653

Synthesis of Tertiary α-Hydroxy Acids by Silylene Transfer to α-Keto Esters

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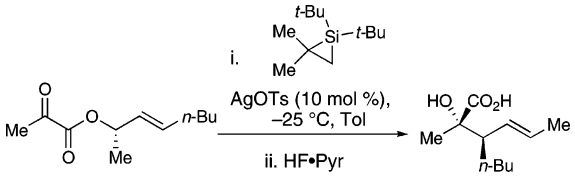
Received August 31, 2007

ABSTRACT

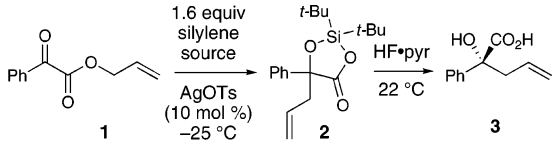


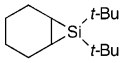
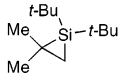
α-Keto esters can be converted into α-hydroxy acids in a single flask involving metal-catalyzed silylene transfer, 6π-electrocyclization, Ireland–Claisen rearrangement, and hydrolysis. This reaction sequence is stereoselective and tolerates alkyl- and aryl-substituted α-keto ester substrates as well as an α-imino ester.

Secondary and tertiary α-hydroxy acids are common substructures in natural products and serve as important synthetic intermediates.[1] Although a number of methods have been developed to prepare secondary α-hydroxy acids,[2] the asymmetric synthesis of tertiary derivatives remains a significant challenge.[3] In this communication, we report a new strategy for the stereoselective, one-flask synthesis of enantiomerically enriched tertiary α-hydroxy acids by silylene transfer to α-keto esters.

Our initial experiments demonstrated that silylene transfer to allylic α-keto esters resulted in direct formation of silalactones. Subjecting ester **1** to silacyclopropane **4** and 10 mol % of AgOTs in toluene provided silalactone **2** in 73% yield as determined by NMR spectroscopy (Table 1).

Table 1. Optimization of the Silylene Source



entry	silylene source	compound	yield (%)[a]
1		**4**	73
2		**5**	80

[a] NMR yield determined using an internal standard ($PhSiMe_3$).

Optimization of the reaction conditions involved temperature and catalyst screens and examination of two different silylene sources.[4] The highest yields were obtained using **5** as the source of silylene in conjunction with AgOTs at reduced temperature.[5] Isolation of the products, however, required refining. All attempts to isolate silalactone **2** provided the silalactone contaminated with the hydrolyzed product **3**.

(1) (a) Coppola, G. M.; Schuster, H. F. *Hydroxy Acids in Enantioselective Synthesis*; Wiley-VCH: Weinheim, 1997. (b) Hanessian, S. *Total Synthesis of Natural Products. The Chiron Approach*; Pergamon: New York, 1983; Chaper 2. (c) Bunte, J. O.; Cuzzupe, A. N.; Daly, A. M.; Rizzacasa, M. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 6376−6380.

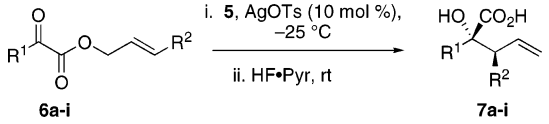
(2) (a) Adam, W.; Lazarus, M.; Boss, B.; Saha-Möller, C. R.; Humpf, H. U.; Schreier, P. *J. Org. Chem.* **1997**, *62*, 7841−7843. (b) Andrus, M. B.; Soma Sekhar, B. B. V.; Meredith, E. L.; Dalley, N. K. *Org. Lett.* **2000**, *2*, 3035−3037. (c) Burk, M. J.; Kalberg, C. S.; Pizzano, A. *J. Am. Chem. Soc.* **1998**, *120*, 4345−4353. (d) Crimmins, M. T.; Emmitte, K. A.; Katz, J. D. *Org. Lett.* **2000**, *2*, 2165−2167. (e) Enomoto, M.; Ito, Y.; Katsuki, T.; Yamaguchi, M. *Tetrahedron Lett.* **1985**, *26*, 1343−1344. (f) Evans, D. A.; Morrissey, M. M.; Dorow, R. L. *J. Am. Chem. Soc.* **1985**, *107*, 4346−4348. (g) Jung, J. E.; Ho, H.; Kim, H.-D. *Tetrahedron Lett.* **2000**, *41*, 1793−1796. (h) Nam, J.; Lee, S. K.; Park, Y. S. *Tetrahedron* **2003**, *59*, 2397−2401. (i) Pansare, S. V.; Ravi, R. G. *Tetrahedron* **1998**, *54*, 14549−14564. (j) Pansare, S. V.; Ravi, R. G.; Jain, R. P. *J. Org. Chem.* **1998**, *63*, 4120−4124. (k) Seebach, D.; Naef, R. *Helv. Chim. Acta* **1981**, *64*, 2704−2708. (l) Tang, L.; Deng, L. *J. Am. Chem. Soc.* **2002**, *124*, 2870−2871. (m) Yu, H.; Ballard, E.; Boyle, P. D.; Wang, B. *Tetrahedron* **2002**, *58*, 7663−7679. (n) He, L.; Byun, H.-S.; Bittman, R. *J. Org. Chem.* **2000**, *65*, 7627−7633.

10.1021/ol702148x CCC: $37.00 © 2007 American Chemical Society
Published on Web 10/02/2007

Purification was simplified by treating the reaction mixture with HF·pyridine[6] to provide analytically pure α-hydroxy acid **3** exclusively after extraction. This procedure obviated the need for chromatography.

Silylene transfer to α-keto esters enabled a stereoselective synthesis of α-hydroxy acids possessing two contiguous stereocenters (Table 2). In all cases, the α-hydroxy acids were formed with ≥97% diastereoselectivity (as determined by ^{1}H NMR spectroscopy), and the relative stereochemistry of each product was assigned by analogy (vida infra). Silylene transfer was general for a range of substrates, although higher yields were obtained with less sterically demanding substrates. In addition, protected allylic and homoallylic alcohols were tolerated (Table 2, entries 8 and 9).

Table 2. Silylene Transfer to a Range of Substrates



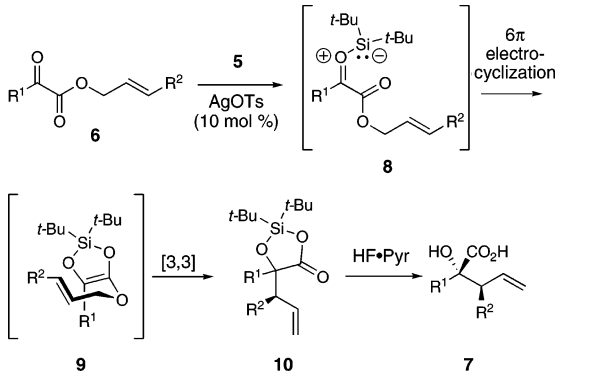
6a-i **7a-i**

entry	R^1	R^2	product	yield (%)[a]
1	Me	Ph	**7a**	70
2	Et	Ph	**7b**	84
3	*i*-Pr	Ph	**7c**	54
4	*t*-Bu	Ph	**7d**	47
5	Ph	Ph	**7e**	71
6	Ph	Me	**7f**	62
7	Ph	*n*-Bu	**7g**	72[b]
8	Ph	$CH_2OTBDMS$	**7h**	71
9	Et	$(CH_2)_2OBn$	**7i**	75

[a] Except where noted, one diastereomer was observed by ^{1}H NMR spectroscopy. [b] A minor isomer (2%) was observed by ^{1}H NMR spectroscopy.

The proposed mechanism for the synthesis of α-hydroxy acids is outlined in Scheme 1. Generation of the silver silylenoid species[4] followed by attack of the ketone carbonyl oxygen leads to silacarbonyl ylide **8**, which can then undergo a 6π-electrocyclization to give silyl ketene acetal **9**. Although this intermediate has not been observed, its viability was demonstrated by the conversion of ethyl pyruvate to a similar silyl ketene acetal under identical silylene transfer conditions (Figure 1).[7] Subsequent Ireland−Claisen rearrangement of silane **9** through a chairlike transition state provides silalactone **10**, which was hydrolyzed to give α-hydroxy acid **7**.[4,8−11]

Scheme 1. Proposed Mechanism



6 **8** **9** **10** **7**

11 **12**

Figure 1. Intermediate silyl ether.

The silylene-mediated synthesis of α-hydroxy acids can be employed to prepare enantiomerically enriched products.[9] α-Keto ester **13**, which was synthesized from commercially available ethyl lactate,[12] was treated under silylene transfer conditions to provide α-hydroxy acid **14** in 77% yield as a single enantiomer (Scheme 2).[13] The relative and absolute stereochemistry of acid **14** was proven by X-ray crystallography of its phenethylamine salt.[12] Remote stereocenters were also observed to influence the configuration of the α-hydroxy acid product. Although the stereocenter of α-keto ester **15** would lie outside the chairlike transition state of the Ireland−Claisen rearrangement, it was able to direct the stereochemical course of the reaction.[14−16]

(3) (a) Fráter, G.; Müller, U.; Günther, W. *Tetrahedron Lett.* **1981**, *22*, 4221−4224. (b) Seebach, D.; Naef, R.; Calderari, G. *Tetrahedron* **1984**, *40*, 1313−1324. (c) Chang, J.-W.; Jang, D.-P.; Uang, B.-J.; Liao, F.-L.; Wang, S.-L. *Org. Lett.* **1999**, *1*, 2061−2063. (d) Picoul, W.; Urchegui, R.; Haudrechy, A.; Langlois, Y. *Tetrahedron Lett.* **1999**, *40*, 4797−4800. (e) Díez, E.; Dixon, D. J.; Ley, S. V. *Angew. Chem., Int. Ed.* **2001**, *40*, 2906−2909. (f) Hutchison, J. M.; Lindsay, H. A.; Dormi, S. S.; Jones, G. D.; Vicic, D. A.; McIntosh, M. C. *Org. Lett.* **2006**, *8*, 3663−3665.

(4) Driver, T. G.; Woerpel, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 9993−10002.

(5) Cleary, P. A.; Woerpel, K. A. *Org. Lett.* **2005**, *7*, 5531−5533.

(6) Trost, B. M.; Caldwell, C. G. *Tetrahedron Lett.* **1981**, *22*, 4999−5002.

(7) Heinicke, J.; Gehrhus, B. *J. Organomet. Chem.* **1992**, *423*, 13−21.

(8) Ando, W.; Hagiwara, K.; Sekiguchi, A. *Organometallics* **1987**, *6*, 2270−2271.

(9) Calad, S. A.; Woerpel, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 2046−2047.

(10) Hiersemann, M.; Nubbemeyer, U. *The Claisen Rearrangement: Methods and Applications*; Wiley-VCH: Weinheim, 2007.

(11) For Claisen rearrangements of α-keto ester derivatives, see: Wood, J. L.; Moniz, G. A.; Pflum, D. A.; Stoltz, B. M.; Holubec, A. A.; Dietrich, H.-J. *J. Am. Chem. Soc.* **1999**, *121*, 1748−1749.

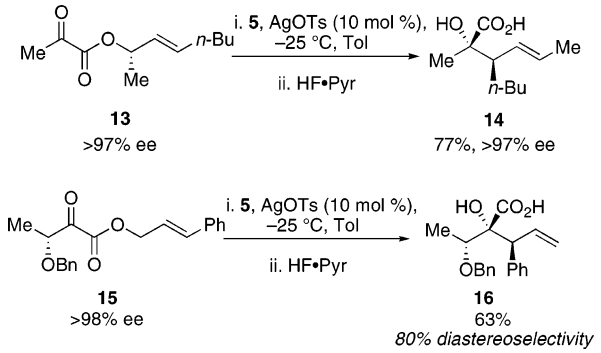
(12) Details are provided as Supporting Information.

(13) Chelation-controlled Ireland−Claisen rearrangements proceed with moderate to high diastereoselectivity: (a) ref 3c. (b) Bartlett, P. A.; Tanzella, D. J.; Barstow, J. F. *J. Org. Chem.* **1982**, *47*, 3941−3945. (c) Hatakeyama, S.; Sugawara, M.; Kawamura, M.; Takano, S. *J. Chem. Soc., Chem. Commun.* **1992**, 1229−1231.

(14) The product was predominantly one diastereomer, but 20% of other compounds can be observed by ^{1}H NMR spectroscopy. These materials are likely to be isomers because the compound exhibits satisfactory elementary analysis.

(15) The relative stereochemistry of the product was assigned based upon analogies to similar systems: Nubbemeyer, U. *Synthesis* **2003**, 961−1008.

Scheme 2. Transfer to Chiral Substrates



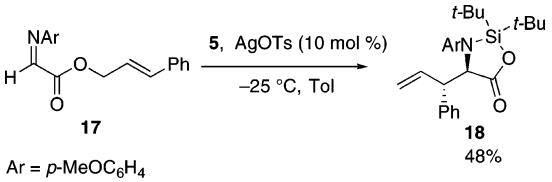


Figure 2. Transfer to the α-imino ester.

Preliminary experiments demonstrate that this method can be extended to the synthesis of α-amino acid derivatives.[17] Silylene transfer to imine **17** provided azasilalactone **18** in an unoptimized 48% yield (Figure 2). In contrast to the α-hydroxy acid synthesis (Table 2), the product was isolated with the silyl protecting group intact. Presumably, the steric bulk of the anisidine moiety prevented hydrolysis during extraction.

In conclusion, α-keto esters can be converted into α-hydroxy acids in a single flask involving metal-catalyzed silylene transfer, 6π-electrocyclization, Ireland−Claisen rearrangement, and hydrolysis. This reaction sequence is stereoselective and tolerates alkyl- and aryl-substituted α-keto ester substrates as well as an α-imino ester.

Acknowledgment. This research was supported by the National Institute of General Medical Sciences of the National Institutes of Health (GM-54909). We thank Stacie Calad (UCI) for her assistance at early stages of the project. K.A.W. thanks Amgen and Lilly for awards to support research. We thank Dr. Joe Ziller (UCI) for X-ray crystallographic data, Dr. Phil Dennison (UCI) for assistance with NMR spectroscopy, and Dr. John Greaves and Ms. Shirin Sorooshian (UCI) for mass spectrometry.

Supporting Information Available: Experimental procedures and spectroscopic, analytical, and X-ray data for the products (PDF, CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

OL702148X

(16) Temmem, O.; Uguen, D.; De Cian, A.; Gruber, N. *Tetrahedron Lett.* **2002**, *43*, 3169−3173.

(17) Kazmaier, U.; Maier, S.; Zumpe, F. L. *Synlett* **2000**, 1523−1535.