Tetrahedron Letters, Vol. 33, No. 5, pp. 585-588, 1992
Printed in Great Britain

0040-4039/92 $3.00 + .00
Pergamon Press plc

A CONVENIENT AND EFFICIENT THREE-STEP SYNTHESIS OF α-CHLORO KETO ACIDS

Ki-Byung Chai and Paul Sampson,*

Department of Chemistry, Kent State University
Kent, Ohio 44242, U.S.A.

Summary. Efficient three-step syntheses of α-chloro keto acids 1a-c from ω-alkenoic acids 2 and ω-alkenyl alcohols 3 are described, proceeding via epoxidation/chloride-mediated epoxide ring opening/Jones oxidation protocols.

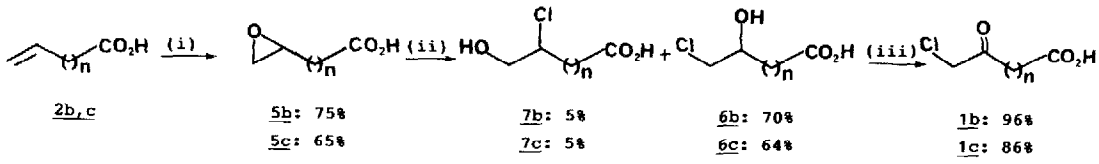
As part of a program aimed at the synthesis of medium-sized carbocyclic rings via transannular condensation reactions within macrocyclic keto lactones,[1] we required efficient access to a series of α-chloro keto acids 1a-c. While a number of methods are available for the preparation of α-chloro ketones,[2] few are of general utility in the synthesis of primary α-chloro ketones. In addition, there is a dearth of synthetic approaches to α-chloro keto acids. Previously, we reported the only synthesis of 10-chloro-9-oxodecanoic acid (1a) to date, proceeding via a route that employed a Ti(III) ion/peroxide-mediated radical addition reaction as the key step.[1] Unfortunately, this route is somewhat inconvenient on a large scale and is only of moderate efficiency. 11-Chloro-10-oxoundecanoic acid (1b) has been reported,[3] but it was prepared in less than 20% overall yield via a five-step protocol that required the use of hazardous diazomethane. Compound 1c has not previously been described.

In this Letter we report new convenient and efficient three-step syntheses of chloro keto acids 1a-c that are amenable to the large scale synthesis of these target compounds. To our knowledge, this epoxidation/regioselective chloride-mediated epoxide ring opening/oxidation protocol has not previously been reported for the conversion of an alkene to an α-chloro ketone. There may be considerable demand for this new methodology. For example, the potent alkylating ability of chloromethyl ketone derivatives of fatty acids has made them attractive as specific enzyme active-site-directed inhibitors.[3] In addition, these compounds should prove useful as intermediates in the synthesis of a variety of other ω-polyfunctional carboxylic acids.[2,3] We have already established their utility in the construction of macrocyclic keto lactones.[1]

In initial studies (see Scheme 1),[4] epoxidation (mCPBA) of ω-alkenoic acids 2b,c[5] gave the epoxy acids 5b,c. Regioselective opening of the epoxide

ring in 5b,c (2M aq. HCl/DMF[8]) gave predominantly the requisite chlorohydrins 6b,c, contaminated with small amounts of the regioisomers 7b,c. These products could be separated by careful column chromatography. Jones oxidation[9] of 6b,c gave the target α-chloro keto acids 1b,c. For convenience, the mixtures of regioisomeric chlorohydrins 6b,c and 7b,c could be carried through the Jones oxidation step without prior separation. The oxidation

Scheme 1 [b: n=8; c: n=9]



2b,c

5b: 75%
5c: 65%

7b: 5%
7c: 5%

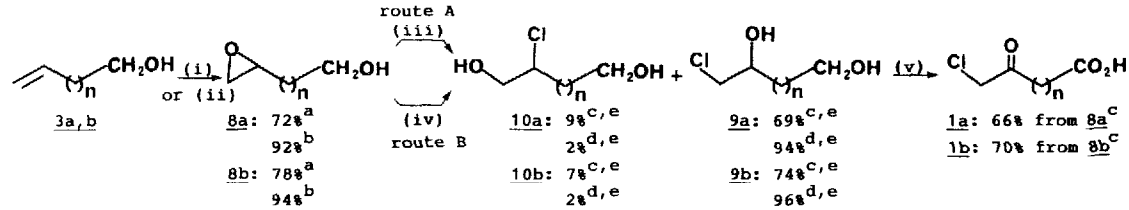
6b: 70%
6c: 64%

1b: 96%
1c: 86%

(i) mCPBA (1.4 eq.), acetone, 25°C, 48 h. (ii) 2M Aq. HCl (1.1 eq.), DMF, 25°C, 3 h. (iii) CrO_3 (1.1 eq.), aq. H_2SO_4, acetone, 25°C, 5 h.

products of the minor regioisomeric chlorohydrins 7b,c were readily separated from the chloro keto acids 1b,c by recrystallization from ether/hexane. This approach to α-chloro keto acids 1b,c was moderately efficient (3 steps and 36-50% overall yield from 2), and was amenable to the preparation of multigram quantities of 1. However, the presence of the carboxyl function caused some difficulties during the separation of the epoxy acids 5b,c from the m-chlorobenzoic acid byproduct of mCPBA epoxidation; careful recrystallization from cold (-40°C) acetone followed by column chromatography was required.

Scheme 2 [a: n=7; b: n=8]



3a,b

8a: 72%[a] 92%[b]
8b: 78%[a] 94%[b]

10a: 9%[c,e] 2%[d,e]
10b: 7%[c,e] 2%[d,e]

9a: 69%[c,e] 94%[d,e]
9b: 74%[c,e] 96%[d,e]

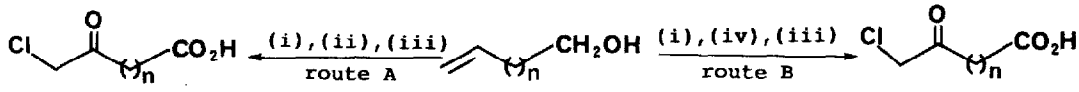
1a: 66% from 8a[c]
1b: 70% from 8b[c]

[a] Reaction performed in acetone (reaction (i)). [b] Reaction performed in CH_2Cl_2 (reaction (ii)). [c] Via route A. [d] Via route B. [e] Yields are of purified mixtures of 9 and 10 after column chromatography. The ratio of 9:10 was established by ^1H NMR spectroscopy.

(i) mCPBA (1.4 eq.), acetone, 25°C, 48 h. (ii) mCPBA (1.1 eq.), CH_2Cl_2, 25°C, 12 h. (iii) 2M Aq. HCl (1.1 eq.), DMF, 25°C, 3 h. (iv) LiCl (1.6 eq.), CH_3COOH (3 eq.), THF, 25°C, 6 h. (v) CrO_3 (3.3 eq.), aq. H_2SO_4, acetone, 25°C, 5 h.

An alternate route was, therefore, devised that would introduce the carboxyl function during the final step (Jones oxidation) of the synthetic sequence (see Scheme 2).[4] Epoxidation (mCPBA) of commercially available and inexpensive ω-alkenyl alcohols 3a,b afforded the epoxy alcohols 8a,b; the use of CH_2Cl_2 rather than acetone as the reaction solvent led to considerably improved yields of 8a,b. The absence of a carboxyl group in 8a,b greatly facilitated removal of the m-chlorobenzoic acid byproduct, which was achieved by a simple aq. $NaHCO_3$ wash. Regioselective opening of the epoxide ring in 8a,b (2M aq. HCl/DMF, route A) gave the requisite chlorohydrins 9a,b, contaminated with small amounts of chromatographically inseparable regioisomeric chlorohydrins 10a,b. Jones oxidation of these mixtures of chlorohydrins afforded the requisite α-chloro keto acids 1a,b; again the oxidation products of the chlorohydrins 10a,b were readily removed by recrystallization. The three-step reaction sequence could be performed on a 10 to 20 g scale without purification of any intermediates (see Scheme 3, route A); the overall yields of chloro keto acids 1 from ω-alkenyl alcohols 3 were 58% (1a) and 64% (1b).

Scheme 3 [**a**: n=7; **b**: n=8]



1a: 58% from 3a[a]
1b: 64% from 3b[a]

3a,b

1a: 80% from 3a[a]
1b: 82% from 3b[a]

[a] Yields are of purified products after recrystallization from ether/hexane. Synthetic intermediates were isolated but not purified.

(i) mCPBA (1.1 eq.), CH_2Cl_2, 25°C, 12 h. (ii) 2M Aq. HCl (1.1 eq.), DMF, 25°C, 3 h. (iii) CrO_3 (3.3 eq.), aq. H_2SO_4, acetone, 25°C, 5 h. (iv) LiCl (1.6 eq.), CH_3COOH (3 eq.), THF, 25°C, 6 h.

A further refinement of this synthetic methodology exploited a new highly regioselective epoxide opening reaction.[10] Treatment of epoxy alcohols 8a,b with LiCl/AcOH/THF (see Scheme 2, route B) gave the requisite chlorohydrins 9a,b in excellent yields and with very high regioselectivity. Incorporation of this protocol into the three-step epoxidation/epoxide ring opening/oxidation reaction sequence (see Scheme 3, route B) (without purification of intermediates) afforded the chloro keto acids 1a,b in 80% and 82% overall yields, respectively, from ω-alkenyl alcohols 3a,b (after recrystallization from ether/hexane). This constitutes an extremely efficient entry to the target chloro keto acids.[11] The use of chloro keto acids 1a-c in the synthesis of macrocyclic keto lactones and medium-sized carbocyclic rings is underway, and will be reported in due course.

Acknowledgements. We would like to thank the American Cancer Society (Ohio Division) and NIH Division of Research Resources (Biomedical Research Support Grant program) for financial support. The NMR spectrometer used in these studies was purchased through an Academic Challenge grant from the State of Ohio. PS thanks The Research Council of Kent State University for a 1991 Summer Research Appointment. KBC acknowledges the Graduate College, Kent State University, for a University Fellowship. We thank Luis F. Rodriguez for performing some large scale experiments in this area.

References.

1. (a) Karim, M.R.; Sampson, P. Tetrahedron Lett. **1988**, 29, 6897. (b) Karim, M.R.; Sampson, P. J. Org. Chem. **1990**, 55, 598.

2. For a recent review of this area, see: De Kimpe, N.; Verhe, R. "The Chemistry of α-Haloketones, α-Haloaldehydes and α-Haloimines"; Patai, S.; Rappoport, Z., Eds.; Wiley: Chichester, 1988; pp 8-24, 126-141.

3. (a) Bloxham, D.P.; Chalkley, R.A. Biochem. J. **1976**, 159, 201. (b) Bloxham, D.P.; Chalkley, R.A.; Coghlin, S.J.; Salam, W. Biochem. J. **1978**, 175, 999. (c) Bloxham, D.P.; Chalkley, R.A.; Cooper, G. In "Methods in Enzymology"; Lowenstein, J.M., Ed.; Academic: New York, 1981; Vol. 72: Lipids, Part D, pp 592-604.

4. Unless otherwise stated, all yields are of isolated and purified material. All new compounds were fully characterized by IR, ^{1}H and ^{13}C NMR spectroscopy, and elemental analysis.

5. 10-Undecenoic acid (2b) is an article of commerce and is inexpensive. Commercial 11-dodecenoic acid (2c) is very expensive, and no convenient literature preparations have been described.[6] We have devised a simple two-step protocol that allows rapid access to compound 2c. Bromination of inexpensive commercial 10-undecen-1-ol (3b) (CBr_4, Ph_3P, Et_2O, 80%) gave 11-bromo-1-undecene (4).[7] Carboxylation of the Grignard reagent derived from 4 ((i) Mg, ether; (ii) CO_2; (iii) H_3O^+; 64%) then afforded 11-dodecenoic acid (2c).

6. (a) An Arndt-Eistert approach requires the use of an excess of hazardous diazomethane: Wotiz, J.H.; Buco, S.N. J. Org. Chem. **1955**, 20, 210; Rountree, J.M.; Smith, J.C. Chem. Ind. **1954**, 190. (b) Pyrolytic approaches involve a five step protocol, or else require reaction temperatures in excess of 500°C: Zakhrkin, L.I.; Churilova, I.M. Izv. Akad. Nauk SSSR, Ser. Khim. **1984**, 2635 (CA 102/131509v).

7. Chen, S.-Y.; Joullie, M.M. Synth. Commun. **1984**, 14, 591.

8. The opening of terminal epoxides using anhydrous HCl in ether or acetone, with moderate to good regioselectivity (3:1 to 8:1), has been reported: Stewart, C.A.; VanderWerf, C.A. J. Am. Chem. Soc. **1954**, 76, 1259. The use of aq. HCl in the absence of an organic solvent (regioselectivity less than 2:1) was also described. These methods are less regioselective and/or less convenient than our room temperature aq. HCl/DMF conditions which, to our knowledge, have not previously been employed for epoxide ring opening.

9. Heilbron, I.; Jones, E.R.H.; Sondheimer, F. J. Chem. Soc. **1949**, 604.

10. Bajwa, J.S.; Anderson, R.C. Tetrahedron Lett. **1991**, 32, 3021.

11. The LiCl/CH_3COOH/THF-mediated conversion of epoxy acid 5b to chlorohydrin 6b also proceeds in excellent yield (88%) and with very high regioselectivity; less than 1% of 7b was obtained. It is likely that a variety of other remote functionality could be tolerated without decreasing the regioselectivity of this reaction. Studies in this area are currently on-going in our laboratory.

(Received in USA 21 August 1991)