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A New Nucleophilic Addition/Ring-Closure Sequence. Enantioselective Synthesis of 3-Deoxy-8-oxatropanes

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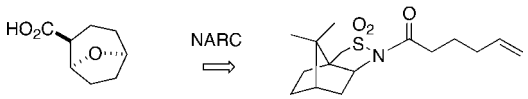
ABSTRACT



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A study of new nucleophilic addition/ring-closure (NARC) sequences has resulted in the development of a stereoselective synthetic route to 3-deoxy-8-oxatropanes. The new sequences consisted of either a syn or anti aldol addition, employing an ω-alkenoyl sultam, followed by two-step bicyclic ring construction involving, consecutively, ring-closing metathesis and intramolecular oxymercuration.

As part of a program directed toward the synthesis and evaluation of new tropane analogues, we required ready access to useful quantities of enantiomerically pure stereoisomers of the previously unreported 8-oxatropanes **1** (Figure 1).[1] We envisaged that these might be available from new nucleophilic addition/ring-closure (NARC) sequences[2] involving stereoselective aldol addition followed by two-step bicyclic ring construction (ring-closing metathesis (RCM) of the resulting diene[3] with, as the final closure, an intramolecular oxymercuration). As shown in Figure 1, two pathways (**a** and **b**) were available depending upon the locus of the alkene.

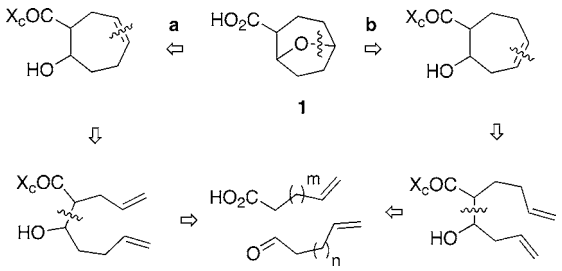

Figure 1. Proposed retrosyntheses of 8-oxatropane **1**.

In previous work, we have demonstrated that the sequence of a nucleophilic addition followed by one or more ring closures (the NARC sequence) provides rapid access to enantiomerically pure mono- and bicyclic structures. Such sequences include asymmetric aldol addition followed by, e.g., (a) an intramolecular 5-*exo*-oxymercuration[4] (monocyclic products), (b) ring-closing metathesis[5] (monocyclic products), or (c) an intramolecular Wacker-type reaction (bicyclic products).[6]

We began this study by selecting pathway **a** for the synthesis of the *exo* isomer **2** (Scheme 1). At the outset of

(1) For reports on the synthesis and biological activity of 8-oxatropanes, see: (a) Meltzer, P. C.; Blundell, P.; Yong, Y. F.; Chen, Z.; George, C.; Gonzalez, M. D.; Madras, B. K. *J. Med. Chem.* **2000**, *43*, 2982. (b) Kozikowsky, A. P.; Simoni, D.; Roberti, M.; Rondanin, R.; Wang, S.; Du, P.; Johnson, K. M. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1831. (c) Eiden, F.; Kainz, A.; Gebhard, R. *Arch. Pharm.* **1992**, *325*, 77.

(2) Perlmutter, P. In *Topics in Current Chemistry*; Metz, P., Ed.; Springer: Heidelberg, 1997; Vol. 190, p 87.

(3) For elegant examples of the application of aldol/RCM sequences to synthesis, see: Crimmins, M. T.; Tabet, E. A. *J. Org. Chem.* **2001**, *66*, 4012 and references therein.

(4) Bratt, K.; Garavelas, A.; Perlmutter, P., Westman, G. *J. Org. Chem.* **1996**, *61*, 2109.

(5) Perlmutter, P.; Rose, M. L. *J. Carbohydr. Chem.* **2002**, *21*, 1.

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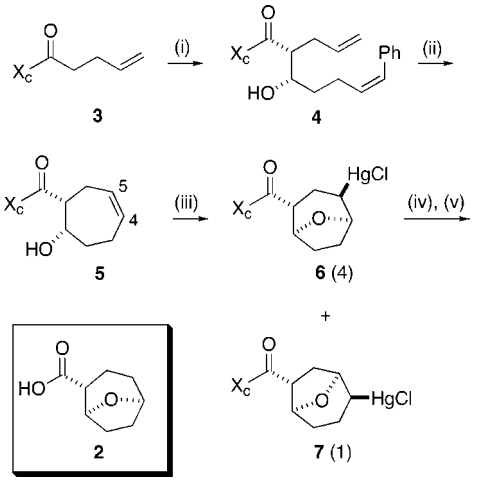
Scheme 1. Synthesis of **2** via Pathway **a**[a]



[a] Reagents and conditions: (i) (a) Et_2BOTf (2.0 equiv), $(^iPr)_2NEt$ (2.2 equiv), CH_2Cl_2, −78 °C, (b) $OHCCH_2CH_2CH{=}CHPh$; (ii) $RuCl_2(CHPh)(PCy_3)_2$, CH_2Cl_2; (iii) (a) $Hg(OCOCF_3)_2$, CH_3CN, (b) satd aq NaCl; (iv) Bu_3SnH, AIBN; (v) LiOH, H_2O_2.

this work, it was not clear what levels of regioselectivity could be obtained in the proposed intramolecular oxymercurations involved in either of the pathways outlined in Figure 1.[7] It appeared plausible that there may be some preference for closure onto C4 of cycloheptene **5** as this would minimize any steric interaction between the nucleophilic alcohol and the adjacent acyl sultam. Thus, **5** was prepared in good yield employing a sequence of *syn*-aldol[8] and ring-closing metathesis (RCM) reactions.

Intramolecular oxymercuration of **5**,[9,10] with either $Hg(II)(OAc)_2$ or $Hg(II)(OCOCF_3)_2$, gave predominantly the product from closure onto C4 (a 4:1 ratio of, respectively, **6** and **7**, Scheme 1**)**. Chloromercurial **6** could be recrystallized pure in 60% yield (its structure is shown in Figure 2).

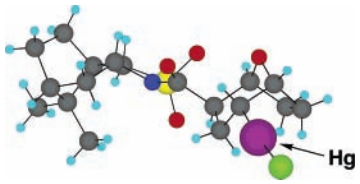
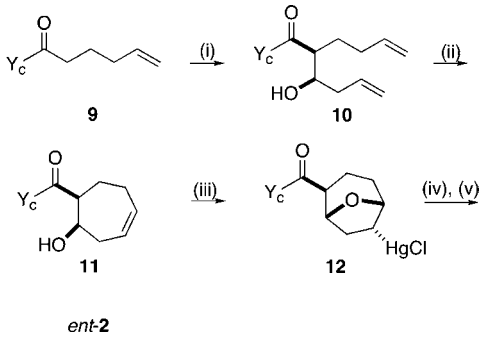


Figure 2. X-ray crystal structure of chloromercurial **6**.

Reductive demercuration[11] followed by hydrolysis[12] then provided enantiomerically pure **2**.

Although the chemistry outlined in Scheme 1 provides a practical route to **2**, the approach was not completely regioselective. Hence, pathway **b** was next explored in a synthesis of the enantiomer of **2**. The synthesis of the next intramolecular oxymercuration candidate, the new cycloheptene **11** (employing Crimmins' method for preparing 3-butenal[13]), proceeded in good overall yield (Scheme 2).

Scheme 2. Synthesis of *ent*-**2** via Pathway **b**[a]

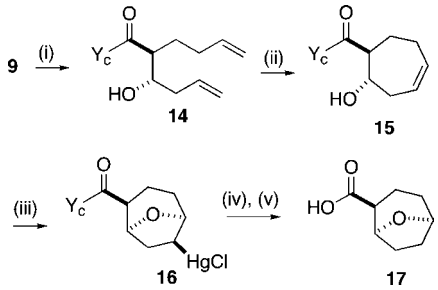


[a] Reagents and conditions: (i) (a) Et_2BOTf (2.0 equiv), $(^iPr)_2NEt$ (2.2 equiv), CH_2Cl_2, −78 °C, (b) $OHCCH_2CH{=}CH_2$; (ii) $RuCl_2(CHPh)(PCy_3)_2$, CH_2Cl_2; (iii) (a) $Hg(OCOCF_3)_2$, CH_3CN, (b) satd aq NaCl; (iv) Bu_3SnH, AIBN; (v) LiOH, H_2O_2.

Treatment of **11** with $Hg(II)(OCOCF_3)_2$ in acetonitrile[14] gave **12** as a single regioisomer in quantitative yield. Reductive demercuration and hydrolysis then gave enantiomerically pure *ent*-**2**.

With pathway **b** established as the preferred route, it was next employed in the synthesis of **17**, one of the enantiomers of the "endo" isomer of **1** (Scheme 3)**.** To prepare **17**, the

Scheme 3. Synthesis of **17** via Pathway **b**[a]



[a] Reagents and conditions: (i) (a) Et_2BOTf (2.0 equiv), $(^iPr)_2Net$ (1.9 equiv), CH_2Cl_2, −78 °C, (b) $OHCCH_2CH{=}CH_2$; (ii) $RuCl_2(CHPh)(PCy_3)_2$, CH_2Cl_2; (iii) (a) $Hg(OCOCF_3)_2$, CH_2Cl_2, (b) satd aq NaCl; (iv) Bu_3SnH, AIBN; (v) LiOH, H_2O_2.

C1-epimer of **11** (i.e., **15**) was required. As shown in Scheme 3, this necessitated employing an *anti*-aldol addition in the first step. Although a number of *anti*-aldol protocols are

(6) (a) Fallon, G. D.; Jones, E. D.; Perlmutter, P.; Selajarern, W. *Tetrahedron Lett.* **1999**, *40*, 7435. (b) Perlmutter, P.; Selajarern, W. *Aust. J. Chem.* **2000**, *53*, 349.

(7) There have been very few reports on intramolecular oxymercurations which produce oxygen-bridged bicyclic products. See: Foehlisch, B.; Joachimi, R. *Chem. Ber.* **1987**, *120*, 1951.

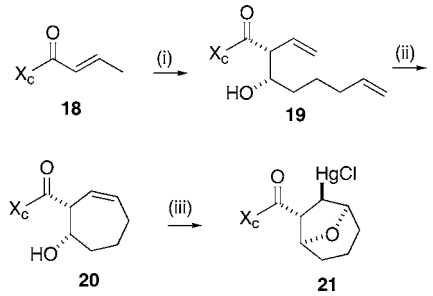
(8) "X_c" in Schemes 1 and 4 is used to represent the (−)-enantiomer of Oppolzer's camphor-derived sultam auxiliary. "Y_c" in Schemes 2 and 3 represents the (+)-enantiomer. See ref 12 for more details on the preparation and use of these auxiliaries.

(9) For reviews on electrophilic cyclisations, see: (a) Robin, S.; Rousseau, G. *Tetrahedron* **1998**, *54*, 13681. (b) Rousseau, G.; Homsi, F. *Chem. Soc. Rev.* **1997**, *26*, 453. (c) Harmange, J. C.; Figadere, B. *Tetrahedron: Asymmetry* **1993**, *4*, 1711.

available,[15] we had noted that the stereoselectivity of aldol additions to 3-butenal was very sensitive to the Lewis acid/Lewis base ratio.[16] By slightly reducing the amount of base present (from 2.2 to 1.9 equiv relative to the acylsultam) while maintaining the diethylboron triflate at 2.0 equiv, we were able to obtain the *anti*-aldol adduct **14** exclusively and in good yield. Intramolecular oxymercuration of the corresponding RCM product **15** was also found to be completely regioselective providing **16** in quantitative yield. Reductive demercuration and hydrolysis then gave enantiomerically pure **17**.

Although we only have very limited evidence at this stage, it appears that, for pathway **b**, if one considers only *exo*-modes of closure in forming bridged products, the 6-*exo*-mode is, not surprisingly, highly favored over the 4-*exo*-mode. Further support for this came from oxymercuration of **20** which gave, exclusively, regioisomer **21** (Scheme 4).

Scheme 4. Regioselective Oxymercuration of Cycloheptene **20**[a]



[a] Reagents and conditions: (i) (a) Et_2BOTf (2.0 equiv), $(^iPr)_2NEt$ (2.2 equiv), CH_2Cl_2, −78 °C, (b) $OHC(CH_2)_3CH{=}CH_2$; (ii) $RuCl_2(CHPh)(PCy_3)_2$, CH_2Cl_2; (iii) (a) $Hg(OAc)_2$, CH_2Cl_2, (b) satd aq NaCl.

In summary, we have developed a new NARC sequence which involves stepwise bicyclic ring construction via ring-closing metathesis and intramolecular oxymercuration. Employing these methods, each of the stereoisomers of oxatropane **1** is now readily available.

Acknowledgment. We thank the Australian Research Council for financial support and Dr. Gary D. Fallon for determining the crystal structure of **6**.

Supporting Information Available: Full details of experimental procedures and spectroscopic and analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) For a recent review on, specifically, electrophile-induced *endo*-cyclizations, see: Knight, D. W. *Prog. Heterocycl. Chem.* **2002**, *14*, 19.

(11) Evans, D. A.; Bender, S. L.; Morris, J. *J. Am. Chem. Soc.* **1988**, *110*, 2506.

(12) Oppolzer, W.; Blagg, J.; Rodriguez, I.; Walther, E. *J. Am. Chem. Soc.* **1990**, *112*, 2767.

(13) Crimmins, M. T.; Kirincich, S. J.; Wells, A. J.; Choy, A. L. *Synth. Commun.* **1998**, *28*, 3675.

(14) **11** failed to react with $Hg(II)(OAc)_2$. For some of the benefits of employing acetonitrile in oxymercurations as solvent, see: Garavelas, A.; Mavropoulos, I.; Perlmutter, P.; Westman, G. *Tetrahedron Lett.* **1995**, *36*, 463.

(15) See: Ghosh, A. K.; Kim, J.-H. *Org. Lett.* **2003**, *5*, 1063 and references therein.

(16) For a recent example of the use of Lewis acid promoted *anti*-aldol reactions, see: Fraser, B.; Perlmutter, P. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2896 and references therein. See also: (a) Heathcock, H. C.; Raimundo, B. C. *Synth. Lett.* **1995**, *12*, 1213. (b) Heathcock, H. C.; Walker, M. A. *J. Org. Chem.* **1991**, *56*, 5747. (c) Heathcock, H. C.; Hansen, M. M.; Danda, H. *J. Org. Chem.* **1990**, *55*, 173.