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Cerium(III) chloride promoted opening of [3.2.1] oxabicycles with methyllithium

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Abstract

Previously reported 1-cyclohexylhydroxymethyl-2,4-dimethyl-8-oxabicyclo [3.2.1]octen-3-ols **2** can be ring opened to produce substituted cycloheptenes **3** in a highly regio- and stereoselective reaction using MeLi in the presence of CeCl₃. These functionalized cycloheptenes contain an array of five contiguous stereocenters which provide access to polypropionate fragments with 1,3,5-*syn,syn* methyl groups. © 1999 Elsevier Science Ltd. All rights reserved.

The [4+3] cycloaddition between furans and oxyallyl cations to produce 8-oxabicyclo[3.2.1]octen-3-ones is a reaction which has become increasingly important in organic synthesis.¹ Ring opening of the [3.2.1]oxabicycles via inter-² and intra-molecular³ strategies leads to highly substituted cycloheptenes which contain stereochemical arrays found in natural products showing diverse biological activity.⁴

We recently disclosed a highly diastereoselective [4+3] cycloaddition between non-racemic cyclohexylfuran-2-ylmethanol and 2,4-dibromopentanone in the presence of diethylzinc to form 1-cyclohexylhydroxymethyl-2,4-dimethyl-8-oxabicyclo[3.2.1]octen-3-one **1**.⁵ Following reduction of the ketone, reductive ring opening (RRO) of **2** provided a functionalized cycloheptene **3** which served as a key building block for the C₁₀₋₁₆ and C₁₇₋₂₃ fragments of ionomycin.^{2f,5} We now wish to report a new additive for nucleophilic ring opening (NRO) of oxabicyclo[3.2.1]octene-3-ol derivatives **2**. Methyllithium, a notoriously unreactive nucleophile,^{2g} works much better after the addition of anhydrous CeCl₃ for NRO on substrates containing an unprotected hydroxyl moiety on the carbon attached to the bridgehead position. The stereochemistry of the side chain hydroxyl is also important.

Oxidative cleavage of the resulting cycloheptenes **3** followed by oxidative removal of the cyclohexylhydroxymethyl side chain would generate an enantiomerically pure polypropionate with a *syn,syn*-1,3,5-trimethyl substitution pattern (Fig. 1), a substructure found in a variety of natural products including denticulatin B,⁶ zincophorin,⁷ oligomycins⁸ and callystatin A.⁹

After examining several parameters (solvent, metal counter-ion, protecting group(s)), we were able to find optimized conditions that led to a high-yielding ring opening of **2**. It was essential that R'=H

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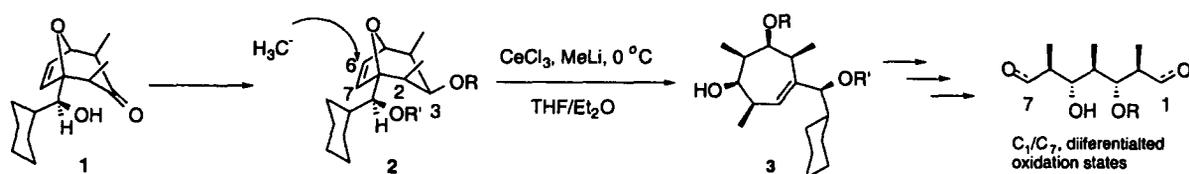


Figure 1.

or else little reaction was observed. In contrast, *R* could be a variety of groups including H or SiR₃. The ring opening of **2a** proceeded cleanly only in the presence of anhydrous CeCl₃, albeit with a large excess of methyllithium over an extended reaction time (see Table 1, entry 1, Cy=cyclohexyl). As expected,^{2a,2g,4b,5} and confirmed by X-ray crystallography, the only ring opened product obtained was with the methyl group added to the exocyclic face of the C₆ position on the [3.2.1]oxabicyclo **2** as demonstrated in Fig. 1.

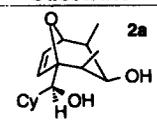
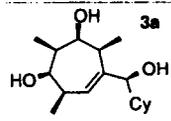
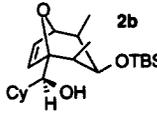
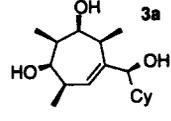
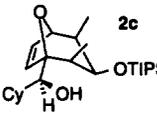
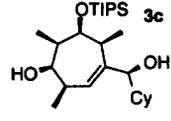
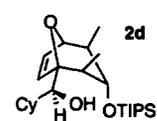
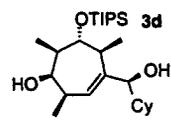
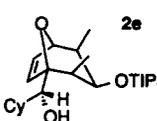
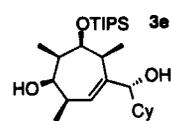
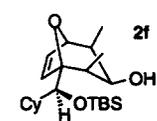
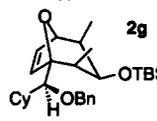
Based on our earlier studies on the effect of protecting groups at the C₃ position,^{2g-h} we investigated various mono- and di-protected derivatives of **2** in the reaction with MeLi and CeCl₃. For example, when the C₃ hydroxyl group was protected as a *tert*-butyldimethylsilyl (TBS) ether, **2b**,¹⁰ a decrease in reaction time and equivalents of MeLi was required (Table 1, entry 2). Unfortunately, the silyl ether was cleaved under the reaction conditions providing **3a** in 67% yield. To prevent this from occurring, the more robust tri-isopropylsilyl (TIPS) group was introduced selectively using TIPSOTf (2.0 equiv.), 2,6-lutidine (2.5 equiv.) in CH₂Cl₂ at 0°C for 2 h to afford **2c** (80–90% yield). Not only did the protecting group prove stable during the reaction, fewer equivalents of both MeLi and CeCl₃ were needed to produce cycloheptene **3c** (72% yield, entry 3a). The reaction was further optimized by including THF as a co-solvent and adjusting the number of equivalents of MeLi and CeCl₃, to ultimately afford **3c** in 80% yield (entry 3b).

The stereochemistry of the C₃ hydroxyl group has little effect on the ring opening reaction, **2d** afforded **3d** in comparable yield (entry 4). However, ring opening of **2e**, where the stereochemistry of the side chain hydroxyl has been inverted by oxidation (pyridinium dichromate in DMF) and selective reduction (LiBH₄, THF), proceeded at a significantly slower rate than **2c**. This implies a combination of conformational and chelation effects may be responsible for the reactivity we observed since chelation by cerium between the side chain hydroxyl and bridging oxygen would be less favored for **2e** because of steric interactions between the cyclohexyl on the side chain and the C₂ methyl of the oxabicyclo. Through a series of protecting group manipulations, compounds **2f** and **2g** were then synthesized. Protection of the hydroxyl group on the side chain results in a loss of reactivity in the presence of MeLi/CeCl₃ (entries 5 and 6). The failure of **2h** to undergo smooth ring opening in the presence of CeCl₃/MeLi (entry 7) proves that the side chain hydroxyl group is essential for the desired ring opening reaction and that the ring opening does not occur with the presence of an alkyl cerium alone. Conformational differences stemming from the di-equatorial methyl groups may also affect the reactivity but we cannot easily assess this issue in a quantitative way.

The reaction did not proceed with MeLi in the presence of other metals such as CuI or ZnI₂ and addition of TMEDA or DABCO did not have a significant affect on the reactivity. Activation of the oxabicyclo with Ni(COD)₂, DIBAL-H, TiCl₄, SnCl₂ or BF₃·OEt₂ followed by treatment with MeLi or MeMgBr was also ineffective.

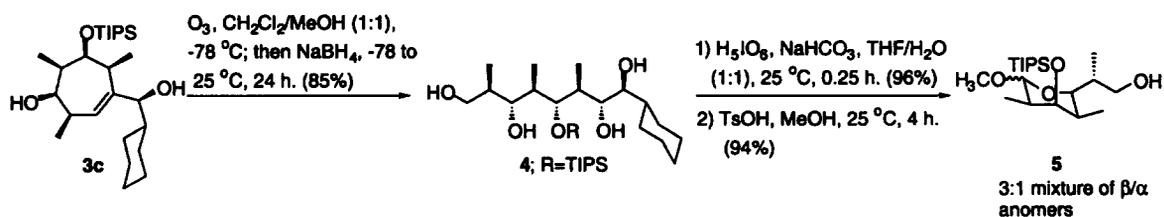
Ring opened product **3c** can be elaborated as shown in Scheme 1. Ozonolysis ruptured the cycloheptene and a reductive work-up with NaBH₄ provided tetraol **4**. Periodate cleavage of the vicinal diol in **4** followed by treatment with methanol and *p*-TsOH acid provides methylated lactol **5** which is the cyclic form of the target polypropionate.

Table 1
Results of the CeCl₃/MeLi opening of [3.2.1]oxabicycles.

| Entry | Substrate | Eq. CeCl ₃ | Eq. MeLi | Conditions | Product | Yield, ^a % |
|-------|---|-----------------------|----------|--|--|-----------------------|
| 1 |  | 5 | 30 | 4 h, 23 °C, Et ₂ O |  | 60 |
| 2 |  | 5 | 20 | 1 h, 23 °C, Et ₂ O |  | 67 |
| 3a |  | 3 | 5 | (a) 0.5 h, 23 °C, Et ₂ O |  | 72 |
| 3b | | 1 | 10 | (b) 1 h, 0 °C, then 0.5 h, 23 °C THF/Et ₂ O (2:1) | | 80 |
| 4 |  | 3 | 5 | 0.5 h, 23 °C, Et ₂ O |  | 70 |
| 5 |  | 1 | 10 | 1 h, 0 °C, then 9 h, 23 °C THF/Et ₂ O (2:1) |  | 50 ^b |
| 6 |  | 3 | 5 | 24 h, 23 °C, Et ₂ O | N.R. | |
| 7 |  | 3 | 5 | 24 h, 23 °C, Et ₂ O | <10% conv. | |
| 8 |  | 3 | 5 | 14 h, 23 °C, Et ₂ O | decomp. | |

^a Isolated yields. ^b Recovered 25% of the starting material 2e.

^a Isolated yields. ^b Recovered 25% of the starting material 2e.



Scheme 1.

In conclusion, we have found a simple procedure which allows 1-cyclohexylhydroxymethyl-2,4-dimethyl-8-oxabicyclo[3.2.1]octen-3-ols to be efficiently ring opened with a very high degree of regio- and stereoselectivity. This represents a substantial enhancement to the oxabicycle methodology developed in our laboratory, providing access to previously unavailable stereoisomers of enantiomerically pure polypropionates with the 1,3,5-methyl groups in a *syn,syn* configuration.

Sample procedure: [1*S*, 2*R*, 3*R*, 4*R*, 5(1*S*), 7*S*]-5-cyclohexylhydroxymethyl-2,4,7-trimethylcyclohept-5-ene-1,3-diol (**3c**). An oven dried Schlenk flask was charged with 'anhydrous' cerium trichloride¹¹ (0.107 g, 0.4 mmol) and a magnetic stir bar. Under an inert atmosphere, a solution of **3c** (0.183 g, 0.4 mmol) in freshly distilled THF (4 mL) was transferred via cannula into the Schlenk flask. The suspension was chilled to 0°C with stirring then treated with methyllithium (1.81 mL, 2.2 mmol, 1.2 M solution in Et₂O). After 1 h another 5 equiv. of methyllithium was added (1.81 mL, solution in Et₂O) and the reaction was allowed to warm to 23°C for 0.5 h. The reaction was then quenched by pouring it slowly on to saturated aqueous solution of Na₄EDTA. The aqueous phase was extracted with CH₂Cl₂ (×3). The combined organic extracts were dried with MgSO₄ and solvent was removed in vacuo. Purification by flash chromatography (EtOAc:Hex gradient; 1:4, 1:3, 1:2, 1:1) provided 0.151 g (80%) of **4c** as a white solid: mp 67–68°C (Et₂O); IR (neat) 3392, 2912, 1658, 1456, 1375, 1074 cm⁻¹; [α]_D²⁵ = +11.2 (c=1.0, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 5.24 (1H, s), 4.21 (1H, d, J=3.7 Hz), 3.80 (1H, d, J=5.1 Hz), 3.58 (1H, d, J=3.6 Hz), 2.63 (1H, q, J=7.0 Hz), 2.44–2.36 (1H, m), 2.21 (1H, s), 2.14–2.04 (1H, m), 1.81–1.55 (6H, m), 1.40–1.27 (1H, m), 1.20–0.88 (5H, m), 1.21 (3H, d, J=7.3 Hz), 1.19 (3H, d, J=7.4 Hz), 1.17 (3H, d, J=7.3 Hz), 1.05 (21H, s); ¹³C NMR (100 MHz, CDCl₃) δ 146.3, 125.6, 77.2, 76.4, 75.6, 73.9, 45.0, 44.9, 43.0, 36.7, 30.7, 27.0, 26.6, 26.5, 26.2, 22.0, 18.3, 18.3, 14.2, 12.8.

Acknowledgements

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References

1. For reviews which include [4+3] cycloadditions and their use in synthesis, see: (a) Lautens, M.; Chiu, P. *Top. Curr. Chem.* **1997**, *190*, 3. (b) Hosomi, A.; Tominaga, Y. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, U.K., 1991; Vol. 5, 593. (c) Mann, J. *Tetrahedron* **1986**, *42*, 4611. (d) Hoffmann, H. M. R. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 1. (e) Noyori, R.; Hayakawa, Y. *Org. React.* **1983**, *29*, 163.
2. (a) Lautens, M.; Klute, W. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 442. (b) Lautens, M.; Ma, S. *J. Org. Chem.* **1996**, *61*, 7246. (c) Lautens, M.; Chiu, P.; Ma, S.; Rovis, T. *J. Am. Chem. Soc.* **1995**, *117*, 532. (d) Arjona, O.; de Dios, A.; Fernandez de la Pradilla, R.; Plumet, J.; Viso, A. *J. Org. Chem.* **1994**, *59*, 3906. (e) Arjona, O.; de Dios, A.; Plumet, J. *Tetrahedron Lett.* **1993**, *34*, 7451. (f) Lautens, M.; Chiu, P.; Colucci, J. T. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 281. (g) Lautens, M.; Chiu, P. *Tetrahedron Lett.* **1993**, *34*, 773. (h) Lautens, M.; Belter, R. *Tetrahedron Lett.* **1992**, *33*, 2617. (i) Lautens, M.; Abd-El-Aziz, A. S.; Lough, A. *J. Org. Chem.* **1990**, *55*, 5305. (j) Lautens, M.; Di Felice, C.; Huboux, A. *Tetrahedron Lett.* **1989**, *30*, 6817.
3. Lautens, M.; Kumanovic, S. *J. Am. Chem. Soc.* **1995**, *117*, 1954.
4. For examples of oxabicyclic compounds as a route to acyclic compounds with multiple stereocenters, see: (a) Arjona, O.; Menchaca, R.; Plumet, J. *Tetrahedron Lett.* **1998**, *39*, 6753. (b) Lautens, M. *Synlett* **1993**, 177.
5. (a) Lautens, M.; Aspiotis, R.; Colucci, J. T. *J. Am. Chem. Soc.* **1996**, *118*, 10930. (b) Colucci, J. Ph.D. Thesis, University of Toronto, 1997.
6. Hochlowoki, J. E.; Faulkner, D. J.; Matsumoto, G. K.; Clardy, J. *J. Am. Chem. Soc.* **1983**, *105*, 7413.
7. Brooks, H. A.; Garoner, D.; Poyser, J. P.; King, T. *J. Antibiot.* **1984**, *37*, 1501.

8. Smith, R. A.; Peterson, W. H.; McCoy, E. *Antibiot. Chemother.* **1954**, *4*, 962. For the structurally related Rutamycins refer to the following: Wuthier, D.; Keller-Schierlein, W.; Wahl, B. *Helv. Chim. Acta* **1984**, *67*, 1208. Thompson, P. Q.; Hoehn, M. M.; Higgins, C. E. *Antimicrob. Agents Chemother.* **1961**, 474.
9. Kobayashi, M.; Higuchi, K.; Murakami, N.; Tajima, H.; Aoki, S. *Tetrahedron Lett.* **1997**, *38*, 2859. For structurally related compounds refer to the following. Anguinomycins: Hayakawa, Y.; Sohda, K.; Shin-ya, K.; Seto, H. *J. Antibiot.* **1995**, *48*, 954. Kazusamycin: Komiyama, K.; Okada, K.; Oka, H.; Tomisaka, S.; Miyano, T.; Funayama, S.; Umezawa, I. *J. Antibiot.* **1985**, *38*, 220. Leptofuranins: Hayakawa, Y.; Sohda, K.; Seto, H. *J. Antibiot.* **1996**, *49*, 980. Leptomycins: Hamamoto, T.; Seto, H.; Beppu, T. *J. Antibiot.* **1983**, *36*, 646. Leptostatin: Abe, K.; Yoshida, M.; Naoki, H.; Horinouchi, S.; Beppu, T. *J. Antibiot.* **1993**, *46*, 735.
10. Aspiotis, R. M.Sc. Thesis, University of Toronto, 1997.
11. Evans, W. J.; Feldman, J. D.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 4581.