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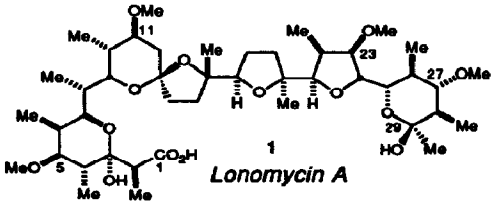
Mild Alcohol Methylation Procedures for the Synthesis of Polyoxygenated Natural Products. Applications to the Synthesis of Lonomycin A

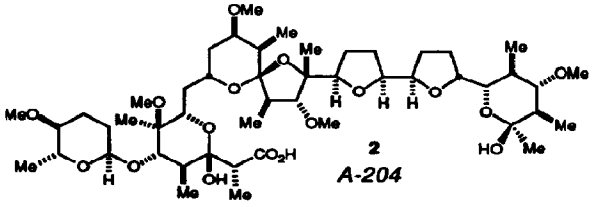
David A. Evans*, Andrew M. Ratz,[1a] Bret E. Huff,[1b] and George S. Sheppard[1b]

Department of Chemistry, Harvard University, Cambridge, Massachusetts 02138, USA

Abstract: Studies directed toward the formation of methyl ethers in key intermediates for the synthesis of lonomycin A are described. Several highly functionalized secondary alcohols have been methylated in excellent yields using the powerful methylating reagents methyl triflate (MeOTf) and trimethyloxonium fluoroborate (Me_3OBF_4).

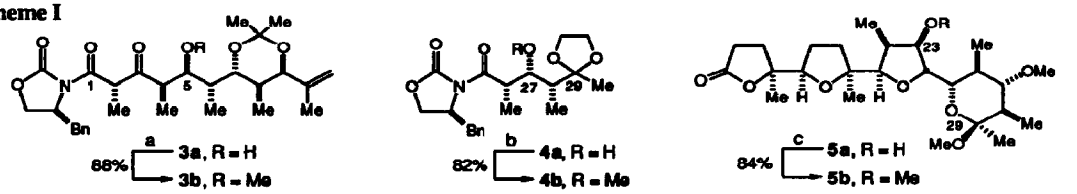
Polyfunctional target structures such as the ionophore antibiotics[2] provide an environment to probe the degree of selectivity that given reagents possess in discriminating between an array of similar functional groups which might be differentiated by either local steric or field effects. In this Letter, we report that hydroxyl groups contained within poly-oxygenated intermediates can be selectively methylated under carefully controlled conditions. These reactions have recently been incorporated into the first total synthesis[3] of lonomycin A and have further implications for the synthesis of related ionophore targets such as A-204 (2).





During the synthesis of the C_1-C_{11} and C_{25}-C_{30} lonomycin A fragments, methylation of the hindered β-hydroxy ketones, **3a** and **4a**, were required (Scheme I). While both **3a** and **4a** are prone to retro-aldol cleavage, **3a** is especially sensitive with respect to epimerization at the β-ketoimide C_2-methyl bearing stereogenic center. Several mild alcohol methylation methods were unsuccessfully explored, including Ag_2O/MeI[4] and the various catalyzed diazomethane procedures.[5] It was ultimately discovered that treatment of **3a** with methyl triflate (15 equiv) and 2,6-di-*tert*-butyl-4-methylpyridine (30 equiv)[6] ($CHCl_3$, 60 °C, 6.5 h) smoothly promoted methylation to give **3b** in 88% yield. Alternatively, the C_{27} alcohol in **4a** was methylated using Me_3OBF_4[7] and 1,8-bis(dimethylamino)naphthalene (Proton Sponge™) (15 equiv each, CH_2Cl_2, 23 °C, 48 h) affording **4b** in 82% yield. Use of these highly activated methylating reagents did not promote alkylation of the oxazolidinone auxiliary to an appreciable extent (<5%) under the indicated reaction conditions.

Scheme I

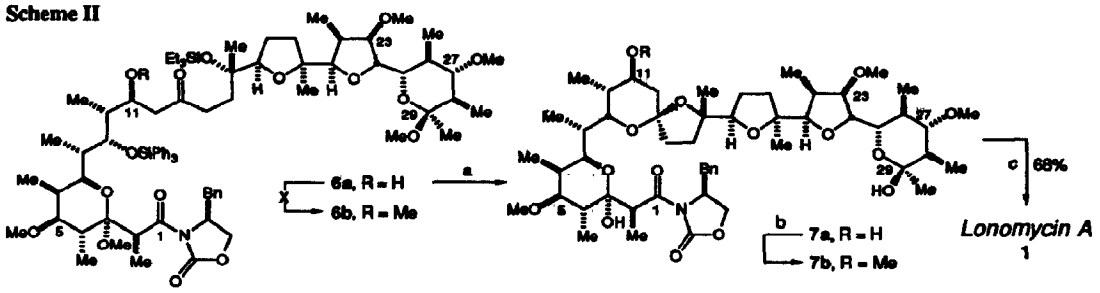


(a) MeOTf, 2,6-di-*t*-butyl-4-methylpyridine, $CHCl_3$, 60 °C. (b) Me_3OBF_4, Proton Sponge™, CH_2Cl_2, 23 °C. (c) As in (b) but 0 °C.

Methylation of the C_{23}-alcohol in **5a** proved to be a considerable challenge. As before, the hindered environment in the vicinity of the alcohol moiety rendered it unreactive to a variety of methylation procedures.[4,5] In particular, the elevated temperature necessary for reaction with methyl triflate caused extensive decomposition, probably due to competitive alkylation of the tetrahydrofuranyl rings.[8] On the other hand, the use of Me_3OBF_4 and Proton Sponge (5 equiv each, CH_2Cl_2, 0 °C, 7 h) efficiently methylated the C_{23} hydroxyl moiety, providing **5b** in 84% yield along with 16% recovered starting material. In this reaction, proper control of temperature was found to be essential to suppress unwanted side reactions.

Completion of the lonomycin synthesis required methylation of the C_{11} alcohol either prior to or after spiroketalization but before the final deprotection events (Scheme II). In spite of extensive efforts to methylate the uncyclized aldol adduct **6a** using the previously mentioned conditions, this transformation could not be achieved without product decomposition. However, the desired transformation was accomplished on the derived spiroketal **7a**. Treatment of **7a** with methyl triflate (25 equiv) and 2,6-di-*tert*-butyl-4-methylpyridine (100 equiv) (CH_2Cl_2, 25 °C, 18 h) selectively alkylated the C_{11}-hydroxyl without competing methylation at either of the C_3 or C_{23} lactol moieties. Presumably both steric and electronic effects are responsible for the observed selectivity in this transformation. Removal of the oxazolidinone auxiliary with LiOOH in THF/H_2O provided synthetic lonomycin A which was identical in all respects (^1H and ^{13}C NMR; IR; TLC; $[\alpha]_D$) to the natural product.

Scheme II



(a) 5 : 86 : 9 48% aqueous HF/CH_3CN/H_2O, 0 °C. (b) MeOTf, 2,6-di-*t*-butyl-4-methylpyridine, 23 °C. (c) LiOOH, THF, H_2O, 0 °C

The preceding alcohol methylations are among the most complex examples recorded in the literature. Although these reactions are quite substrate dependent, the observation that surprisingly high levels of selectivity can be achieved in these poly-oxygenated intermediates is significant. In general, our observations are consistent with the fact that Me_3OBF_4 is a somewhat more reactive methylating reagent than MeOTf.[8] In the individual reactions described, the choice of both methylating reagent and reaction conditions was predicated on gaining the proper level of selectivity for the desired hydroxyl functionality.[9] The full details of the total synthesis of lonomycin A will be reported shortly.

References and Notes

1) (a) Department of Defense Predoctoral Fellow (b) National Institutes of Health Postdoctoral Fellow
2) Evans, D. A.; Polniaszek, R. P.; DeVries, K. E.; Guinn, D. E.; Mathre, D. J. *J. Am. Chem. Soc.* **1991**, *113*, 7613-7630 and references cited therein.
3) For a preliminary communication see: Evans, D. A.; Sheppard, G. S. *J. Org. Chem.* **1990**, *55*, 5192-5194.
4) Greene, A. E.; Drian, C. L.; Crabbe, P. *J. Am. Chem. Soc.* **1980**, *102*, 7583-7584.
5) (a) Ohno, K.; Nishiyama, H.; Nagase, H. *Tetrahedron Lett.* **1979**, *20*, 4405-4406. (b) Smith, A. B. III; Hale, K. J.; Laakso, L. M.; Chen, K.; Rieva, A. *Tetrahedron Lett.* **1989**, *30*, 6963-6966.
6) Walba, D. M.; Thurmes, W. N.; Haltiwanger, R. C. *J. Org. Chem.* **1988**, *53*, 1046-1056.
7) Meerwein, H.; Hinz, G.; Hofmann, P.; Kronig, E.; Pfeil, E. *J. Prakt. Chem.* **1937**, *147*, 257.
8) Stang, P. J.; Hanack, M.; Subramanian, L. R. *Synthesis* **1982**, 85-126.

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