ORGANIC LETTERS

2002
Vol. 4, No. 11
1879−1882

Total Synthesis of Ionomycin Using Ring-Opening Strategies

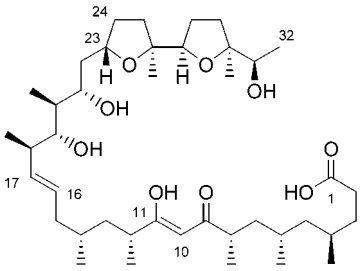
Mark Lautens,* John T. Colucci, Sheldon Hiebert, Nicholas D. Smith, and Giliane Bouchain

Davenport Research Laboratories, Department of Chemistry, University of Toronto, 80 St. George St., Toronto, Ontario M5S 3H6, Canada

mlautens@chem.utoronto.ca

Received March 13, 2002

ABSTRACT



Ionomycin

The total synthesis of the polyether antibiotic ionomycin, a calcium ionophore, is described. The synthesis demonstrates the utility of ring-opening methodologies as applied to the synthesis of polypropionate and deoxypolypropionate subunits, which are found in two of the four fragments in the synthesis.

Ionomycin, isolated in 1978 from *Streptomyces conglobatus*,[1] belongs to a class of natural products known as polyether antibiotics. The ability to chelate inorganic cations and transport them across lipid membranes has made these "ionophores" of significant interest. Ionomycin is unique among this family because of its high affinity for binding calcium and as such has been used extensively in neurochemistry as a tool for studying the effects of increasing intracellular Ca^{2+} concentrations.[1c]

The structure of calcium-bound ionomycin was elucidated by Gougoutas and co-workers in 1979.[2] It is highly oxygenated, as is typical of the polyether antibiotics. The presence of the two acidic functionalities, the terminal carboxylic acid and the β-diketone, allows the formation of the 1:1 complex with Ca^{2+}. It also contains three hydroxyl groups and two tetrahydrofuran rings in addition to 14 stereogenic centers, making ionomycin a challenging synthetic target.

Two previous total syntheses have been published by the Evans and Hanessian labs.[3] Both groups used synthetic strategies they developed for the synthesis of polypropionate and deoxypolypropionate subunits. Evans used the well-developed chiral enolate chemistry, and Hanessian applied the chiron approach using L-glutamic acid as the intial source of chiral information. Our goal was to show the utility of the ring-opening of oxabicyclic alkenes as an alternative and/or complementary approach to the synthesis of these structural motifs.

Our retrosynthetic analysis of ionomycin is similar to that of the Evans and Hanessian syntheses. The three points of disconnection are at the β-diketone, the trans olefin, and the first tetrahydrofuran ring (Scheme 1). We realized that the presence of the 1,3 *syn*-dimethyl moiety, which is present in three of the four fragments, made this molecule ideal for

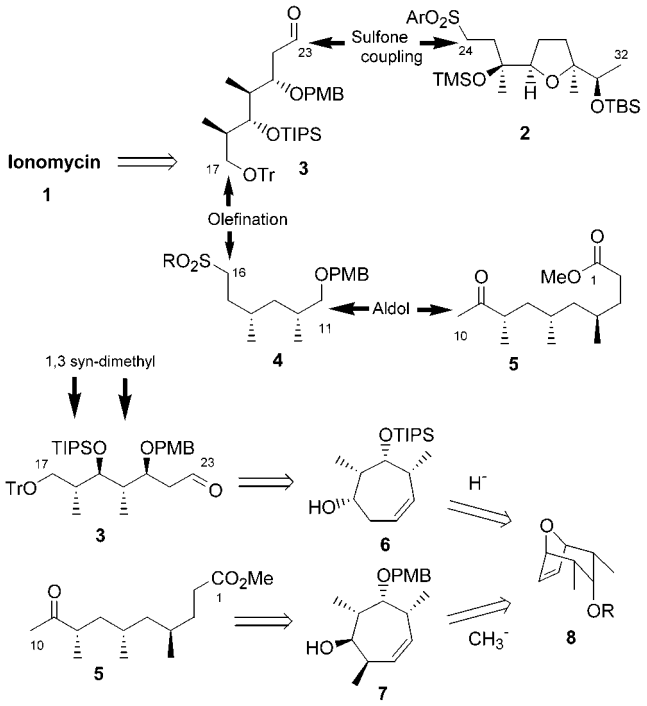
(1) (a) Liu, C.-M.; Hermann, T. E. *J. Biol. Chem.* **1978**, *253*, 5892. (b) Liu, W.-C.; Slusarchyk, D. S.; Astle, G.; Trejo, W. H.; Brown, W.; Meyers, E. *J. Antibiot.* **1978**, *31*, 815. (c) Parpura, V.; Basrsky, T. A.; Liu, F.; Jeftinija, K.; Jeftinija, S.; Haydon, P. G. *Nature* **1994**, *369*, 744.

(2) Toeplitz, B. K.; Cohen, A. I.; Funke, P. T.; Parker, W. L.; Gougoutas, J. Z. *J. Am. Chem. Soc.* **1979**, *101*, 3344.

(3) (a) Dow, R. L. Ph.D. Dissertation, Harvard University, 1985. (b) Evans, D. A.; Dow, R. L.; Shih, T. L.; Takacs, J. M.; Zahler, R. *J. Am. Chem. Soc.* **1990**, *112*, 5290. (c) Hanessian, S.; Cooke, N. G.; DeHoff, B.; Sakito, Y. *J. Am. Chem. Soc.* **1990**, *112*, 5276.

10.1021/ol025872f CCC: $22.00
Published on Web 05/08/2002

Scheme 1



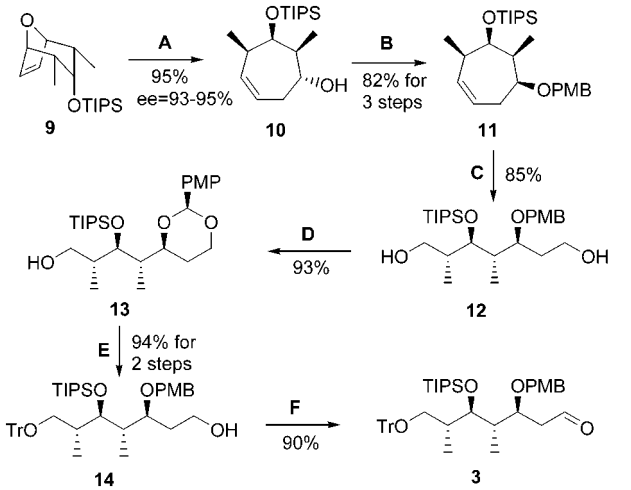
the use of the ring-opening methodologies developed in our labs. In particular, fragments **3** and **5** can both be obtained from the [3.2.1] oxabicyclic alkene **8**.

Fragment **3** can be synthesized from **6**, which is readily prepared from an asymmetric addition of a hydride to **8**. The asymmetric reductive ring opening was developed in our labs using a nickel-catalyzed addition of DIBAL-H to the oxabicycle.[4] Likewise, fragment **5** can be obtained from **7**, which comes from an asymmetric addition of a methyl group to **8**. A palladium-catalyzed asymmetric addition of a dialkylzinc to an oxabicyclic alkene was recently developed in our group[5] and could be used to carry out this transformation.

The [3.2.1] oxabicyclic alkenes are easily prepared by a [4 + 3] cycloaddition between furan and an oxyallylcation.[6] These substrates have been widely used to gain access to both cyclic and acyclic molecules.[7] Their rigid bicyclic structure can be used to introduce functional groups in a highly stereoselective manner. If this functional group introduction occurs in an S_N2' fashion with ring opening of the bridging oxygen bond, cycloheptenes with four or five contiguous stereocenters can be obtained.

The utility of the asymmetric reductive ring opening is powerfully shown in the synthesis of the $C_{17}-C_{23}$ fragment (Scheme 2), where three of the four stereocenters in the fragment are set using the ring-opening reaction. A slow addition of DIBAL-H to **9** and the $Ni(COD)_2$/(*S*)-BINAP catalyst in toluene at 65 °C gave **10** in 95% yield and 93−95% ee. The configuration of the hydroxyl at C_{21} needed to be inverted in order to set the final stereocenter. Swern oxidation and then reduction with DIBAL-H at −78 °C, which proceeded with >30:1 selectivity, readily achieved this goal. The hydroxyl was then protected as a PMB ether to give **11** in 82% for the three steps.

Scheme 2[a]



[a] (**A**) 5 mol % $Ni(COD)_2$, 10 mol % (*S*)-BINAP, toluene, 65 °C, 1.1 equiv of DIBAL-H (added over 20 h); (**B**) (a) DMSO, $(COCl)_2$, NEt_3, CH_2Cl_2, −78 °C; (b) PhMe, DIBAL-H, −78 °C; (c) THF, KHMDS, PMBCl; (**C**) O_3, MeOH/CH_2Cl_2, −78 °C then $NaBH_4$, rt; (**D**) CH_2Cl_2, DDQ, mol sieves, rt; (**E**) (a) TrCl, NEt_3, DMAP, CH_2Cl_2; (b) CH_2Cl_2, DIBAL-H, −78 to O °C; (**F**) DMSO, $(COCl)_2$, NEt_3, CH_2Cl_2, −78 °C.

The cycloheptene ring was then cleaved by ozonolysis to the dialdehyde, and after reductive workup diol **12** was obtained in 85% yield. The critical task of differentiating the two ends of the acyclic subunit was then addressed. The problem was solved by employing a strategy previously used by Oikawa,[8] who showed that oxidation of the benzylic position of a *p*-methoxybenzyl ether under anhydrous conditions in the presence of an appropriately positioned hydroxyl group would result in cyclization onto the cation to form an acetal. When diol **12** was treated with DDQ in anhydrous dichloromethane, selective cyclization occurred to afford the PMP acetal **13** in 93% yield.

With the ends of the acyclic fragment differentiated the other hydroxyl could now be protected as a trityl ether.

(4) (a) Lautens, M.; Chiu, P.; Ma, S.; Rovis, T. *J. Am. Chem. Soc.* **1995**, *117*, 532. (b) Lautens, M.; Rovis, T. *J. Am. Chem. Soc.* **1997**, *119*, 11090.

(5) (a) Lautens, M.; Renaud, J.-L.; Hiebert, S. *J. Am. Chem. Soc.* **2000**, *122*, 1804. (b) Lautens, M.; Hiebert, S.; Renaud, J.-L. *Org. Lett.* **2000**, *2*, 1971. (c) Lautens, M.; Hiebert, S.; Renaud, J.-L. *J. Am. Chem. Soc.* **2001**, *123*, 6834.

(6) Lubineau, A.; Bouchain, G. *Tetrahedron Lett.* **1997**, *38*, 8031. For reviews on [4 + 3] cycloadditions, see: (a) Hosomi, A.; Tominaga, Y. *Comprehensive Organic Synthesis*; Trost, B., Fleming, I., Paquette, L. A., Eds.; Pergamon: Oxford, U.K., 1991; Vol. 5, Chapter 5.1, p 593. (b) Hoffmann, H. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 1. (c) Noyori, R.; Hayakawa, Y. *Org. React.* **1983**, *29*, 163.

(7) For reviews on S_N2' and S_N2'-like ring opening of oxa-*n*-cyclo systems, see: (a) Vogel, P.; Cossy, J.; Plumet, P.; Arjona, O. *Tetrahedron* **1999**, *55*, 13521. (b) Woo, S.; Keay, B. *Synthesis* **1996**, 669. (c) Lautens, M. *Synlett* **1993**, 177.

(8) Oikawa, Y.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1982**, *23*, 885.

Regioselective reduction of the acetal under Takano's protocol[9] using DIBAL-H gave the alcohol **14** in 94% yield for the two steps. Finally, Swern oxidation of the primary alcohol gave aldehyde **3** in 90% yield and completed the synthesis of the $C_{17}-C_{23}$ fragment in 12 steps from furan in 19.6% overall yield.

Whereas the stereochemistry in the $C_{17}-C_{23}$ fragment was set by an asymmetric addition of hydride to the oxabicycle, the C_1-C_{10} fragment requires the introduction of a methyl group at the C_4 position. This is accomplished using the asymmetric nucleophillic ring opening catalyzed by a chiral palladium catalyst.

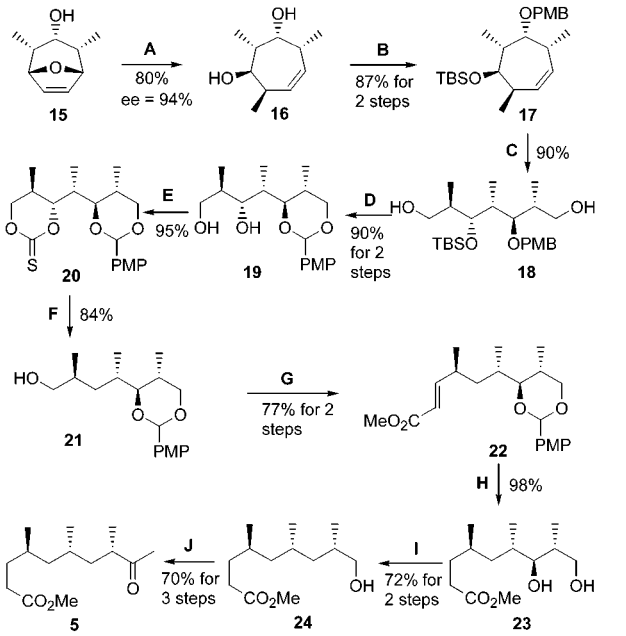
The chiral catalyst, formed from a 1:1 mixture of $Pd(CH_3CN)_2Cl_2$ and the chiral ligand (*R*)-*i*Pr-(*R*)DIPOF,[10] was used together with 10 mol % $Zn(OTf)_2$ for the addition of Me_2Zn to oxabicycle **15** in refluxing dichloroethane. The product cycloheptendiol **16** containing the 1,3,5-trimethyl subunit with complete diastereocontrol was obtained in 80% yield and 94% ee (Scheme 3). The two hydroxyl groups could now be selectively protected as the *tert*-butyldimethylsilyl ether and *p*-methoxybenzyl ether in 92% and 95% yields, respectively, to give **17**.

The cycloheptene olefin was now cleaved by ozonolysis to give the acyclic fragment **18** in 90% yield. The differentiation of the two hydroxyl groups was carried out as in the $C_{17}-C_{23}$ fragment. Treatment of **18** with DDQ in anhydrous dichloromethane gave selective formation of a single PMP acetal and after TBAF deprotection of the silyl ether gave diol **19** in 90% for the two steps. This diol was treated with thiocarbonyl diimidazole (TCDI) to give a 95% yield of the cyclic thiocarbonate **20** in order to set up the deoxygenation. Barton has shown that these cyclic thiocarbonates undergo radical-induced reduction to yield preferentially the primary alcohol as a result of the greater stability of the secondary radical upon collapse of the intermediate during the deoxygenation.[11] Employing Barton's protocol the primary alcohol **21** was obtained in 84% yield.

A two-carbon extension was then carried out using a stabilized Wittig reagent on the aldehyde obtained by TPAP oxidation of alcohol **21**. The overall yield of **22** was 77%. Hydrogenation catalyzed by Pd/C led to reduction of the olefin and removal of the PMP acetal to give diol **23** in 98% yield.

Removal of the remaining secondary hydroxyl group was achieved in an identical fashion as before using Barton's protocol. Formation of the thiocarbonate took place in 90% yield, while reduction gave the primary alcohol **24** in 80% yield. Finally, conversion of the primary alcohol to the methyl ketone **5** was achieved in three steps. Oxidation to the aldehyde by TPAP/NMO was followed by addition of MeMgBr in THF at −78 °C to give a mixture of isomers. A Dess−Martin oxidation gave ketone **5** and completed the synthesis of the C_1-C_{10} fragment in 18 steps from furan in 6.9% yield.

Scheme 3[a]



[a] (**A**) 5 mol % Pd[(R)-*i*Pr-(R)-DIPOF]Cl_2, 10 mol % $Zn(OTf)_2$, 2.5 equiv of Me_2Zn, dichloroethane, reflux; (**B**) (a) TBDMSCl, imidizole, DMF; (b) NaH, PMBBr, Bu_4NI (cat.), DMF; (**C**) O_3, MeOH/CH_2Cl_2, −78 °C then $NaBH_4$, rt; (**D**) (a) CH_2Cl_2, DDQ, mol sieves, rt; (b) TBAF, THF, rt; (**E**) TCDI, THF, 50 °C; (**F**) Bu_3SnH, AIBN (cat.), toluene, reflux; (**G**) (a) TPAP (cat.), NMO, CH_2Cl_2, rt; (b) $MeO_2CCH{=}PPh_3$; (**H**) H_2, $Pd(OH)_2$, MeOH; (**I**) (a) TCDI, THF, 50 °C; (b) Bu_3SnH, AIBN (cat.), toluene, reflux; (**J**) (a) TPAP (cat.), NMO; (b) MeMgBr, THF; (c) Dess−Martin oxidation.

With all four fragments in hand efficient methods of coupling were explored.[12] The formation of the $C_{23}-C_{24}$ bond was carried out using a sulfone anion addition to aldehyde **3** (Scheme 4). The product **25** was obtained as a mixture of diastereomers, and the phenyl sulfone could now be removed by a two-step oxidation/α-reduction sequence. Oxidation to ketone **26** was accomplished by a TPAP/NMO oxidation, and then SmI_2 was used to reductively remove the α-phenyl sulfone[13] to give **27** in 61% for the three steps.

Formation of the *trans* tetrahydrofuranyl ring was projected to occur via a diastereoselective substrate-controlled reduction of the ketone followed by activation and intramolecular S_N2 etherification. For the reduction we chose to use a diastereoselective samarium-mediated Tishchenko reaction developed by Evans.[14] This reaction involves the reduction of *β*-hydroxy ketones using SmI_2 in the presence of benzaldehyde (as the hydride source) to yield benzyloxy alcohols with high *anti* selectivities (typically 90−99%).

(9) Takano, S.; Akiyama, M.; Sato, S.; Ogasawara, K. *Chem. Lett.* **1983**, 1593.

(10) For the synthesis of 2(*R*)-(diphenylphosphino)-1-[4(*R*)-isopropyl-2-oxazolinyl]ferrocene (abbreviated as *i*-Pr-DIPOF), see: (a) Richards, C.; Locke, A. *Tetrahedron: Asymmetry* **1998**, *9*, 2377. (b) Nishibayashi, Y.; Uemura, S. *Synlett* **1995**, 79.

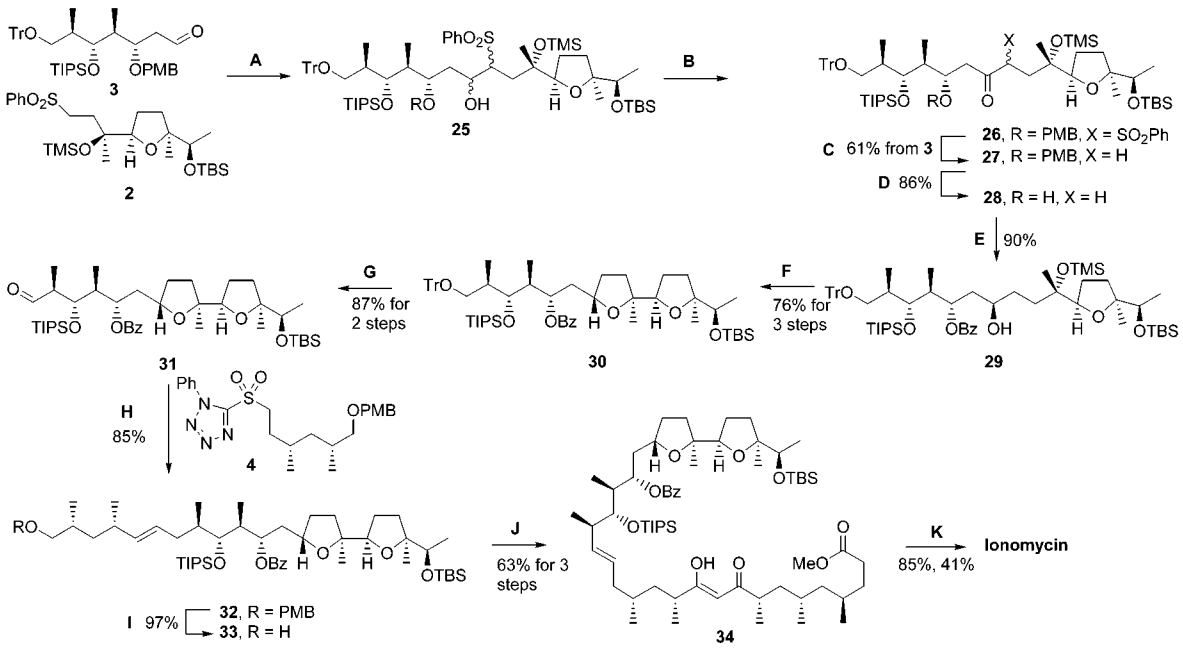
(11) (a) Barton, D. H. R.; Subramanian, R. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1718. (b) Barton, D. H. R.; McCombie, S. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574.

(12) The synthesis of the other fragments along with other approaches to the coupling strategy will be discussed in a forthcoming paper.

(13) Molander, G. A.; Hahn, G. *J. Org. Chem.* **1986**, *51*, 1135.

(14) Evans, D. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1990**, *112*, 6447.

Scheme 4[a]



[a] (**A**) **2** + BuLi then **3**, THF, −78 °C; (**B**) TPAP (cat.), NMO, mol sieves, CH_2Cl_2; (**C**) SmI_2, MeOH, THF, −78 °C; (**D**) DDQ, H_2O, CH_2Cl_2; (**E**) 26 mol % SmI_2, 5 equiv of PhCHO, THF, −10 °C; (**F**) (a) TsCl, DMAP (cat.), CH_2Cl_2; (b) 1 M HCl, THF, 0 °C; (c) NaH, THF, 50 °C; (**G**) (a) $Pd(OH)_2$, C_6H_{12}, EtOH, reflux; (b) TPAP (cat.), NMO, mol sieves, CH_2Cl_2; (**H**) KHMDS, **4**, then add to **31**, THF, −78 °C to rt; (**I**) DDQ, H_2O, CH_2Cl_2, O°C; (**J**) (a) DMSO, $(COCl)_2$, NEt_3, CH_2Cl_2, −78 °C; (b) Bu_2BOTf, $(i\text{-}Pr)_2(Et)N$, **5**, then add to aldehyde from **33**, CH_2Cl_2, −78 °C; (c) CrO_3·Pyr, Celite, CH_2Cl_2; (**K**) (a) HF, H_2O, MeCN, rt; (b) LiOH, H_2O, DME, 80 °C, 7 h.; (c) $CaCl_2$, H_2O, pH 9.

The *β*-hydroxy ketone **28** was obtained in 86% yield by an oxidative removal of the PMB ether with DDQ. Application of Evans' protocol on **28** using 26 mol % SmI_2 provided hydroxy benzoate **29** in 90% yield with no other isomer detectable by ^{1}H NMR. The alcohol could now be activated by formation of the tosylate under standard conditions. The TMS ether was then removed with dilute HCl, and the crude hydroxy tosylate was treated with NaH in THF at 50 °C to yield the bis tetrahydrofuranyl product **30** in 76% yield for the three steps. Finally, the trityl ether was removed, and oxidation of the alcohol to the aldehyde **31** was carried out in order to set up coupling with the $C_{11}-C_{16}$ fragment.

Incorportation of the $C_{11}-C_{16}$ fragment required selective formation of the *trans* $C_{16}-C_{17}$ double bond. A Julia−Lythgoe olefination[15] is known to provide predominantly *trans* olefins, particularily when there is α branching on the aldehyde and/or sulfone. Both the Hanessian and Evans' syntheses utilized this protocol, but we found that using the same reaction with **31** and the phenyl sulfone analogue of **4** gave poor yields and selectivities. We therefore looked at newer variants of the Julia reaction and found that the use of the 1-phenyl-1*H*-tetrazol-5-yl sulfone developed by Kocienski and co-workers[16] gave the best results. When sulfone **4** was treated with KHMDS and then added to aldehyde **31,** formation of olefin **32** took place in 85% yield (exclusively *trans* olefin by ^{1}H NMR).

The final coupling involved an aldol reaction between fragment **5** and the aldehyde obtained from alcohol **33**. The boron aldol reaction developed by Evans and Dow in their synthesis provided us with the aldol product accompanied by loss of the TBS protecting group. When the same reaction was used with a modified workup procedure, however, the silyl ether remained intact. After a Collins oxidation the *β*-diketone **34** was obtained in 63% yield for the three steps.

Deprotection of the silyl ethers and hyrolysis of the two esters were also carried out using procedures slightly modified from those used in the Evans synthesis. Final treatment with $CaCl_2$ gave ionomycin as the calcium salt, which was identical to a commercially obtained sample.

Acknowledgment. We thank the Ontario Research and Development Fund, NSERC (Canada), Merck Frosst, and the University of Toronto for financial support of this work. S.H. thanks NSERC for financial support in the form of a postgraduate fellowship.

Supporting Information Available: Experimental procedures and full characterization for compounds **1**−**34**, as well as syntheses of fragments **2** and **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL025872F

(15) (a) Julia, M.; Paris, J.-M. *Tetrahedron Lett.* **1973**, *14*, 4833. (b) Kocienski, P. J.; Lythgoe, B.; Ruston, S. *J. Chem. Soc., Perkin Trans. 1* **1978**, 829. (c) Kocienski, P. J.; Lythgoe, B.; Waterhouse, I. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1045.

(16) Blakemore, P. R.; Cole, W. J.; Kocienski, P. J.; Morely, A. *Synlett* **1998**, 26.