Total Synthesis

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A Synthesis of an Ionomycin Calcium Complex**

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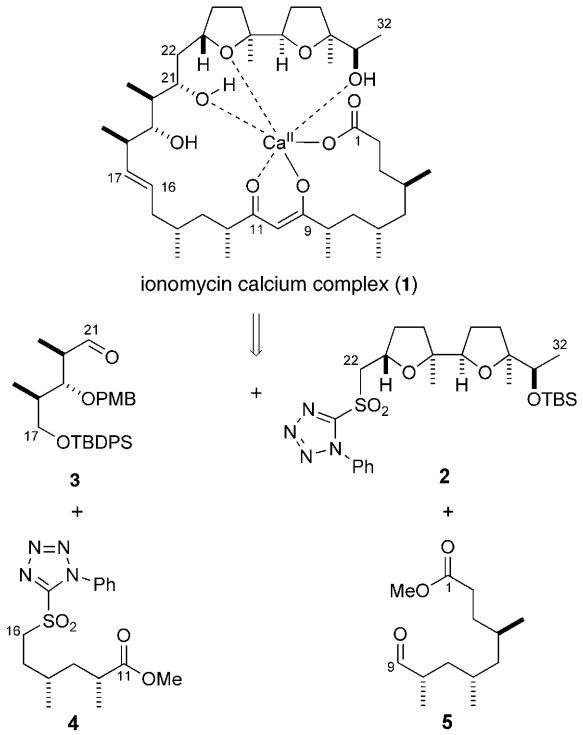
Ionomycin is a narrow-spectrum ionophore antibiotic isolated from *Streptomyces conglobatus*.[1] X-ray crystallographic analysis of its calcium complex (**1**; see Scheme 1)[2] revealed a carboxylic acid group and an unusual β-diketone moiety which, in combination, are responsible for its avidity for divalent cations. Ionomycin has little value as an antibiotic but it is widely used as a tool in cell biology for the investigation of processes requiring calcium mobilization.[3] The three total syntheses reported to date exemplify the utility of chiral enolate chemistry (Evans et al.),[4] the chiron approach (Hanessian et al.),[5] and asymmetric ring-opening of symmetrical 8-oxabicyclo[3.2.1]oct-6-enes (Lautens et al.)[6] for the construction of polypropionate chains. In addition, numerous fragment syntheses have also been reported.[7] Herein, we describe a synthesis of ionomycin and its calcium complex (**1**) from four key fragments **2**–**5** (Scheme 1). Our synthesis features: 1) the use of a stereoselective gold(III)-catalyzed cycloisomerization of an α-hydroxyallene to create a dihydrofuran ring, and 2) the use of a rhodium-catalyzed rearrangement of an α-diazo-β-hydroxyketone to generate the β-diketone moiety.

Our synthesis began with the construction of the C22–C32 bis(tetrahydrofuran) fragment **2**. Thus, addition of lithium TMS-acetylide to the known aldehyde **6**[8] gave a racemic propargylic alcohol which was oxidized to the corresponding ketone **7** using pyridinium dichromate (Scheme 2). The asymmetric hydrogen-transfer reaction of ketone **7** by the method of Noyori and Ohkuma[9] led to (*R*)-**9** in 95% yield and e.r. = 97:3, as determined by ^{1}H NMR spectroscopic analysis of the mandelate ester. Simultaneous cleavage of the TMS and acetate groups using potassium carbonate in methanol resulted in a water soluble diol (*R*)-**10**. This species underwent Sharpless asymmetric epoxidation to form the epoxide intermediate **11**, which spontaneously cyclized to the tetrahydrofuran **12**. The primary hydroxy group was then removed by tosylation and subsequent reduction using lithium triethylborohydride gave the secondary alcohol **14**, which was protected as its TBS silyl ether **15**.



Scheme 1. Structure and retrosynthetic analysis of the ionomycin calcium complex (**1**). PMB = *p*-methoxybenzyl, TBDPS = *tert*-butyldiphenylsilyl, TBS = *tert*-butyldimethylsilyl.

Addition of the freshly prepared aldehyde **16** to the titanium derivative of alkyne **15** gave the desired propargylic alcohol **17** (*anti*/*syn* = 6:1) in accord with the Felkin–Anh model of asymmetric induction (Scheme 3).[10] The corresponding mesylate **18** was treated with $MeCu{\cdot}MgBr_2{\cdot}LiCl$ by an *anti*-selective S_N2' mechanism[11] to give allene **19** (d.r. = 6:1) in 93% yield. Selective removal of the isopropylidene group was accomplished using 0.10 M PPTS in isopropanol at 50 °C to give a mixture of diastereomeric diols (6:1), which were separated by column chromatography. Pure diol **20** was isolated in 53% overall yield (63% brsm) for the four steps starting from alkyne **15**. In the key step of the sequence, the diol **20** was treated with 1 mol% $AuCl_3$ in THF at room temperature to afford the dihydrofuran **21** as a single diastereoisomer in 92% yield. By using the donor solvent THF in the cyclization, decomposition and removal of the TBS group were minimized.[12] To complete the sequence, the alkene in **21** was hydrogenated and the primary alcohol

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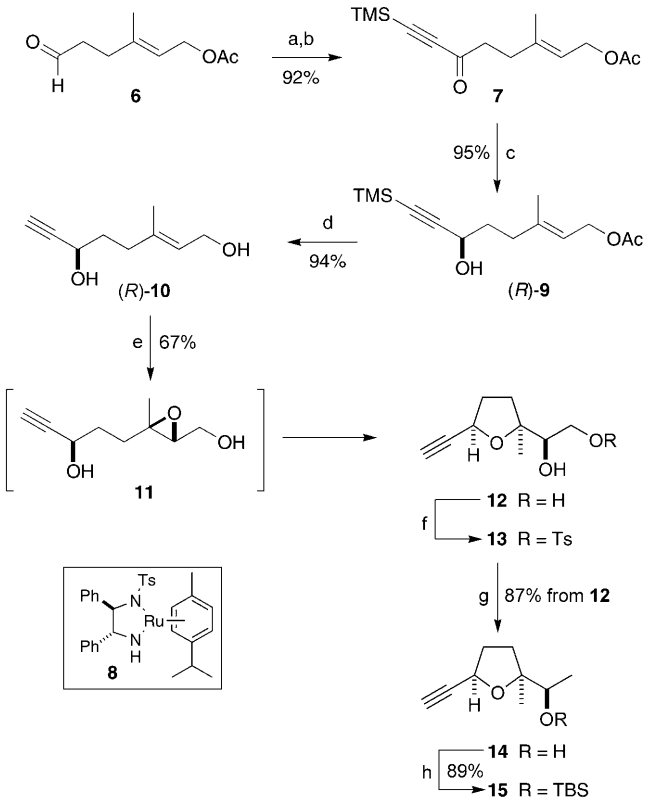
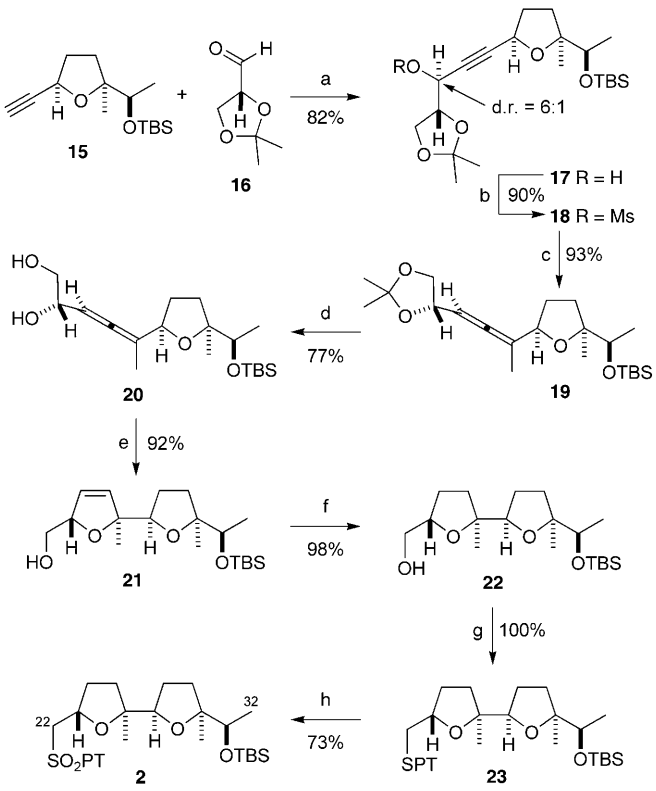


Scheme 2. Synthesis of alkyne **15**. Reagents and conditions: a) TMS-acetylene, *n*BuLi, THF, −78 °C, 30 min; then add **6**, −78 °C, 2 h, 96%; b) PDC, CH_2Cl_2, RT, 40 h; c) **8** (0.010 equiv), *i*PrOH, 20 h, 90% (over 2 steps), e.r. 97:3; d) K_2CO_3, MeOH, RT, 2 h; e) (−)-DIPT, $Ti(O\text{-}iPr)_4$, *t*BuOOH, CH_2Cl_2, −20 °C, 12 h, 63% (over 2 steps); f) Bu_2SnO, TsCl, Et_3N, CH_2Cl_2, RT, 17 h; g) $LiBHEt_3$, THF, −10 °C; h) TBSOTf, Et_3N, CH_2Cl_2, 0 °C, 77% (over 3 steps). DIPT = diisopropyl tartrate, PDC = pyridinium dichromate, THF = tetrahydrofuran, TMS = trimethylsilyl, Ts = 4-toluenesulfonyl.

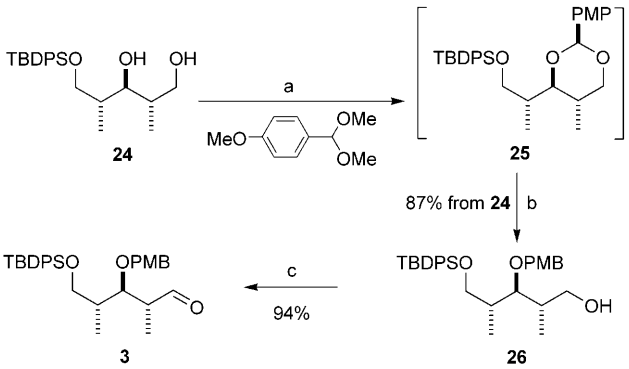


Scheme 3. Synthesis of the bis(tetrahyrdofuran) fragment **2**. Reagents and conditions: a) **15**, *n*BuLi, THF, −65 °C; then add $ClTi(O\text{-}iPr)_3$, −78 °C → −60 °C, 90 min; then add **16**, −78 °C → −40 °C, 2 h, 82% (97% brsm), d.r. = 6:1; b) MsCl, Et_3N, CH_2Cl_2, 0 °C, 90%; c) MeMgCl/LiBr/CuBr (1:1:1), THF, −60 °C, 50 min; then warm to −20 °C, 93%, d.r. = 6:1; d) PPTS, *i*PrOH, 50 °C, 2.5 h; then separate diastereoisomers by chromatography, 77% of pure **20**; e) 1 mol% $AuCl_3$, THF, RT, 30 min, 92%; f) H_2, 10% Pd/C, MeOH, 98%; g) 1-phenyl-1*H*-tetrazole-5-thiol, DIAD, Ph_3P, THF, RT, 2 h; h) *m*CPBA, $NaHCO_3$, CH_2Cl_2, 24 h, 73% (over 2 steps). brsm = based on recovered starting material, DIAD = diisopropylazodicarboxylate, *m*CPBA = *m*-chloroperbenzoic acid, Ms = methanesulfonyl, PT = 1-phenyl-1*H*-tetrazolyl, PPTS = pyridinium *p*-toluenesulfonate.

subjected to a Mitsunobu reaction with 1-phenyl-1*H*-tetrazole-5-thiol. Oxidation of the resultant thioether **23** with *m*CPBA gave the crystalline 1-phenyl-1*H*-tetrazolyl sulfone **2**, whose structure and configuration were established by X-ray crystallography.

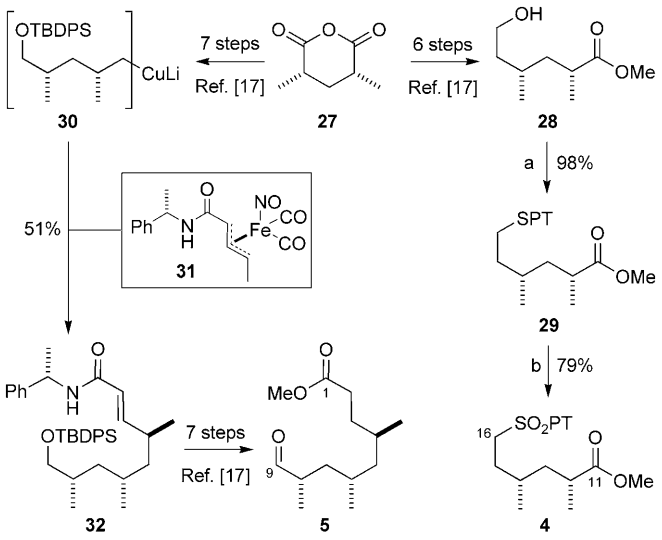
The synthesis of fragment **3** is summarized in Scheme 4. Diol **24**,[13] prepared according to the protocol of Kishi and coworkers,[14] was converted into its *p*-methoxyphenyl acetal derivative **25** by an acetal exchange process. The acetal **25** underwent regioselective reductive cleavage using DIBAL-H[15] to give the primary alcohol **26**. Finally, oxidation of the primary alcohol with Dess–Martin periodinane gave the aldehyde **3** in 94% yield.

The readily available *meso*-3,5-dimethylglutaric anhydride (**27**)[16] is a common precursor for the synthesis of fragments **4** and **5** (Scheme 5). Thus, anhydride **27** was converted into the phenyltetrazolyl sulfone **4** in eight steps via the known alcohol **28**.[17] A noteworthy step in the synthesis of fragment **5** was the construction of the stereogenic centre at C4 by the nucleophilic addition of the cuprate **30** to the neutral η^3-allyliron complex **31**. After oxidative decomplexation of the iron, the enamide **32** was obtained in 51% yield.[17]



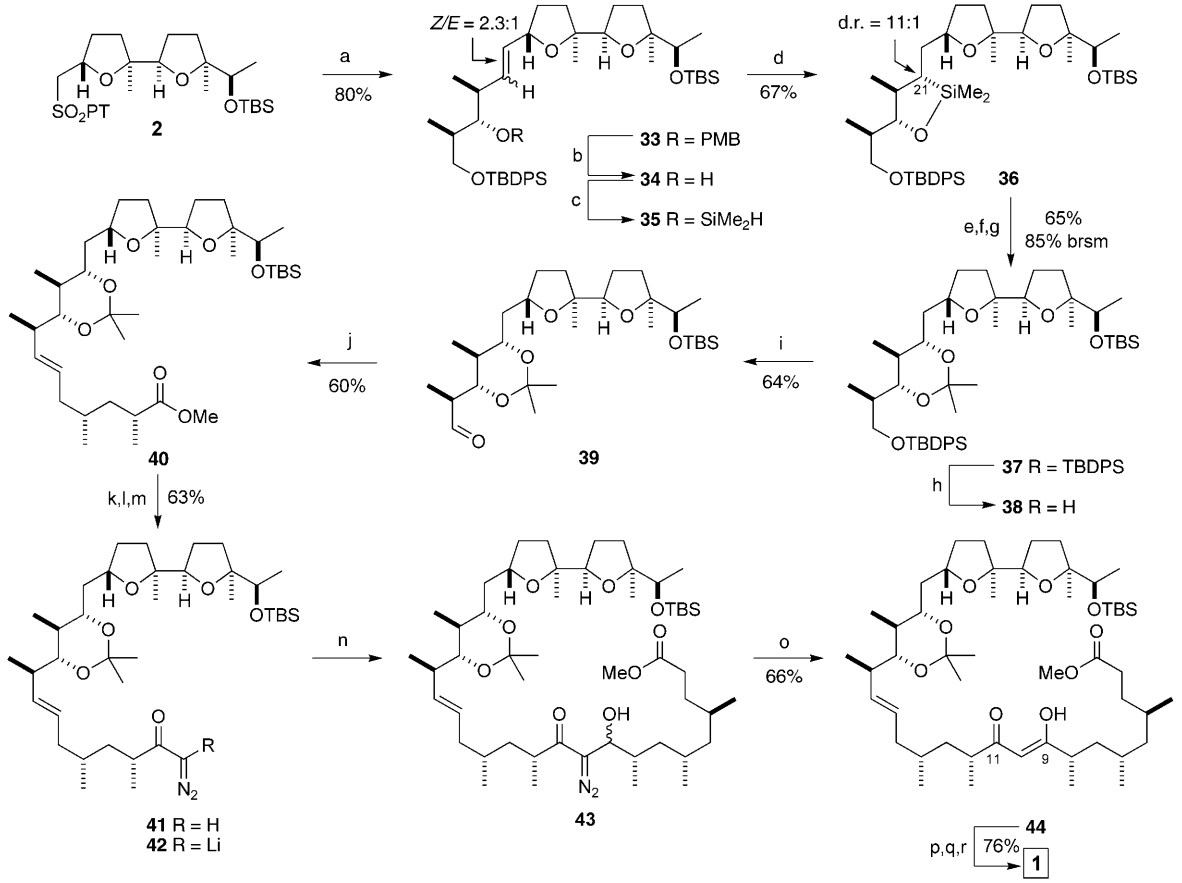
Scheme 4. Synthesis of fragment **3**. Reagents and conditions: a) PPTS, CH_2Cl_2, RT; b) DIBAL-H, −60 °C → RT, 87% (over 2 steps); c) DMP, py, CH_2Cl_2, 94%. DIBAL-H = diisobutylaluminium hydride, DMP = Dess–Martin periodinane, PMP = *p*-methoxyphenyl, py = pyridine.

With all four fragments **2**–**5** in hand, all that remained to complete the synthesis was to link them sequentially



Scheme 5. Synthesis of fragments **4** and **5**. Reagents and conditions: a) PTSH, DIAD, Ph_3P, THF, RT, 98%; b) *m*CPBA, CH_2Cl_2, 79%.

(Scheme 6). Fragments **2** and **3** were coupled through a Julia–Kocienski olefination.[18] The reaction proceeded in good yield but a mixture of double-bond isomers **33** was generated with an excess of the *Z* isomer (*Z*/*E* = 2.3:1). The mixture was converted into the dimethylsilyl ethers **35**, which underwent an easy intramolecular Pt-catalyzed hydrosilylation.[19] To obtain a good diastereomeric ratio (11:1) for the reaction it was required that both the *E* and *Z* isomers reacted with a similar stereochemical bias in favor of the desired siloxane **36**.[20] The isomers were separated by column chromatography and the major siloxane **36** (67% from **35**) was oxidized in DMF by using the protocol developed by Tamao (30% H_2O_2, KOH).[21] Unfortunately, the oxidation was accompanied by partial removal of the TBDPS group, thus the TBDPS group had to be restored so that the remaining 1,3-diol could be protected as its isopropylidene derivative to give **37** in 65% overall yield (85% brsm) from **36**. Selective cleavage of the TBDPS group in the presence of the secondary TBS ether was accomplished by treatment of **37** with NaOH powder in DMF, and the resultant primary alcohol was oxidized with TPAP/



Scheme 6. Completion of the total synthesis of ionomycin calcium complex (**1**). Reagents and conditions: a) add LHMDS (1.1 equiv) to a mixture of **2** (1.0 equiv) and **3** (1.6 equiv) in THF, −78 °C, 1 h; then warm to 0 °C, 80%; b) DDQ, CH_2Cl_2/H_2O, RT, 80 min; c) Me_2SiHCl, Et_3N, CH_2Cl_2, RT, 10 min; d) $Pt(DVTMS)_2$ (0.00044 equiv), *n*-hexane, RT, 10 min, 67% (over 2 steps); e) KOH, 30% H_2O_2, DMF, RT, 2 h; f) TBDPSCl, imidazole, DMF, H_2O, RT; g) $Me_2C(OMe)_2$, PPTS (cat.), RT, 85% brsm (over 3 steps); h) powdered NaOH, DMF, RT, 18 h, 70%; i) TPAP, NMO, CH_2Cl_2, RT, 15 min, 92%; j) add KHMDS to a mixture of sulfone **4** and aldehyde **39** in THF, −78 °C, 1 h; then warm to RT, 60%; k) LiOH, THF/MeOH/H_2O (2:2:1); l) $(COCl)_2$, DMF (0.3 mol%), CH_2Cl_2, RT; m) CH_2N_2, Et_2O, 63% (over 3 steps); n) LDA added to **41** (1.0 equiv) and **5** (2.7 equiv), THF, −78→−20 °C; o) $[Rh_2(OAc)_4]$ (8 mol%), DME, RT, 20 min, 66% (over 2 steps); p) HF, MeCN/H_2O, RT; q) LiOH, DME/H_2O (10:1), RT; r) $CaCl_2$, pH 8 buffer, 76% (over 3 steps). DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, DME = 1,2-dimethoxyethane, DMF = *N*,*N*-dimethylformamide, DVTMS = 1,3-divinyltetramethyldisiloxane, HMDS = hexamethyldisilazane, LDA = lithium diisopropylamide, NMO = *N*-methylmorpholine *N*-oxide, TPAP = tetra-*n*-propylammonium perruthenate.

NMO to give aldehyde **39** in 64% yield (from **37**). A second Julia–Kocienski olefination[18] was then used to append fragment **4** and forge the C16–C17 *E*-alkene **40** exclusively.

In their total syntheses of ionomycin, Evans,[4] Hanessian[5], and Lautens[6] generated the β-diketone moiety spanning C9–C11 by consecutive boron-mediated aldol and Cr^{VI} oxidation reactions. We exploited a protocol devised by Pellicciari et al.[22] based on α-diazocarbonyl chemistry. The requisite α-diazoketone **41** was synthesized in three steps from ester **40** (Scheme 6). Lithium diisopropylamide (2 equiv) was added to a mixture of aldehyde **5**[17] and α-diazoketone **41** at −78 °C. The metalated α-diazoketone **42**, which was generated in situ, was added to the aldehyde to form the β-hydroxy-α-diazoketone **43** after aqueous work-up, and was then treated with $[Rh_2(OAc)_4]$ (3 mol%) in DME at room temperature. The resultant carbene inserted into the adjacent C–H bond to generate the β-diketone **44** in 66% overall yield from **41**. The ^1H and ^{13}C NMR spectra of **44** were identical to the data reported by Evans et al.[4] Finally, the TBS ether and isopropylidene groups were removed from **44** with aqueous HF and the methyl ester was hydrolyzed with LiOH to give ionomycin, which was isolated as its crystalline calcium salt. ^1H and ^{13}C NMR spectroscopic data for our synthetic material were identical to those of a commercial sample of the ionomycin calcium salt. The structure was also confirmed by X-ray analysis of our synthetic material, which was recrystallized from heptane (see the Supporting Information).

In conclusion, we have accomplished a synthesis of ionomycin calcium complex (**1**) in 33 steps from aldehyde **6** in 0.68% overall yield. Noteworthy features of our approach include: 1) an efficient asymmetric synthesis of an allene using a copper(I)-mediated *anti*-selective S_N2' reaction (**18**→**19**), 2) a highly stereoselective gold(III)-catalyzed cycloisomerization reaction of an α-hydroxyallene to a 2,5-dihydrofuran (**20**→**21**),[23] and 3) the construction of the β-diketone moiety by a rhodium-catalyzed rearrangement of an α-diazo-β-hydroxyketone (**43**→**44**). Our synthesis of ionomycin provides further evidence for the value of gold-catalyzed cycloisomerization reactions in the construction of complex natural products.[24]

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