A Formal Synthesis of Ionomycin Featuring a Permanganate-Mediated Oxidative Cyclisation

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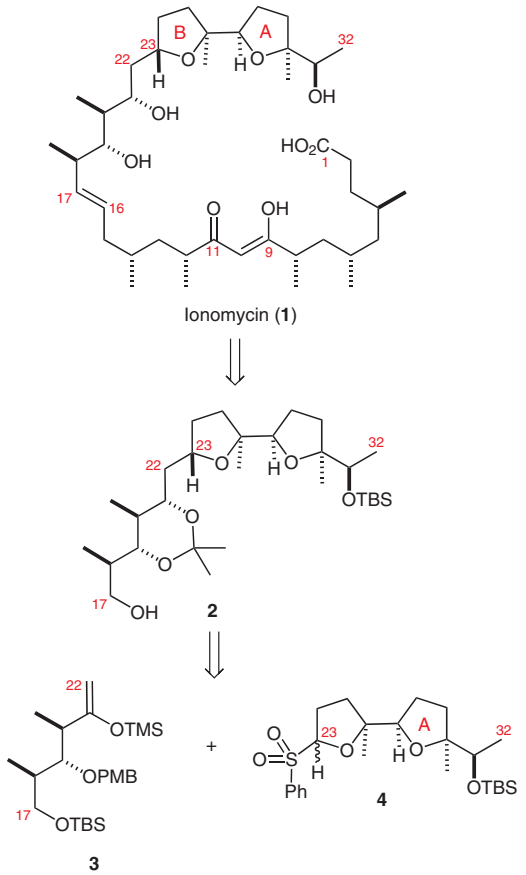
Abstract: Key steps in a synthesis of the C17–C32 fragment of ionomycin are (a) an auxiliary-directed oxidative cyclisation of a diene with potassium permanganate to construct a tetrahydrofuran ring and four stereogenic centres in a single operation, and (b) a chain-appendage reaction featuring the alkylation of an enolsilane by an oxocarbenium ion generated from a 2-phenylsulfonyl-substituted tetrahydrofuran.

Key words: ionomycin, permanganate oxidation, directed reduction, crotylboration, carbocupration

Ionomycin (**1**) is an ionophore isolated from *Streptomyces conglobatus* with a high affinity for divalent cations.[1–3] A detailed competitive binding study revealed the following selectivity: $Pb^{2+} > Cd^{2+} > Zn^{2+} > Mn^{2+} > Ca^{2+} > Cu^{2+} > Co^{2+} > Ni^{2+} > Sr^{2+}$.[4] It is widely used as a tool in cell biology for the investigation of processes requiring calcium mobilisation and its use in lead detoxification has been mooted. In 2009 we reported a total synthesis of ionomycin and its calcium complex based on (a) a highly stereoselective Au^{3+}-catalysed cycloisomerisation of an α-hydroxyallene to create the tetrahydrofuran B, and (b) a rhodium-catalysed rearrangement of an α-diazo-β-hydroxyketone to generate the β-diketone moiety.[5] A key intermediate in our synthesis was the C17–C32 alcohol **2** (Scheme 1), which had also featured in the preceding syntheses developed by Evans[6] and Hanessian[7] reported in 1990.[8] We now report an alternative synthesis of the C17–C32 alcohol **2**, and hence a formal synthesis of ionomycin, which features (a) a permanganate-mediated oxidative cyclisation reaction[9] to create the tetrahydrofuran ring A in fragment **4** and four of its stereogenic centres in a single operation, and (b) a Ley α-heteroalkylation reaction to append fragment **3** to C23 of fragment **4**.

The *anti*,*anti*-stereotriad in fragment **3** was installed by a crotylmetallation reaction on the known aldehyde **8** (Scheme 2).[10] Initial attempts to use Roush's easily accessible tartrate-derived (*E*)-crotylboronic ester reagent **9** were thwarted by poor diastereoselectivity (dr = 2:1).[11–13] Better results were obtained with (*E*)-crotyldiisopinocampheylborane (**10**) derived from (+)-α-pinene; in this case the desired adduct **11** was obtained in a modest 52% yield but excellent diastereoselectivity (dr >95:5).[14] The yield and diastereoselectivity of the crotylmetallation reaction were very sensitive to the quality of the reagent **10**, with the best results being obtained with freshly prepared reagent.[15] After protection of the secondary alcohol as its *p*-methoxybenzyl ether, the alkene function of **12** was converted into the ketone **13** through a Wacker oxidation.[16] Finally, the ketone was converted into its enolsilane derivative in the usual way, to afford fragment **3** in 30% overall yield from commercial ester **5**.

Our synthesis of the sulfone fragment **4** was predicated on an auxiliary-directed diastereoselective oxidative cyclisation of the (*Z*,*Z*)-diene **18** (Scheme 3). A related reaction had previously featured as a key step in our synthesis of salinomycin.[17] The C26,27-trisubstituted alkene was sourced from inexpensive neryl acetate, but the C30,31-trisubstituted alkene required construction. Neryl acetate (**14**) was first converted into the terminal alkyne **15** in six steps as previously described (35% overall).[17] An efficient



Scheme 1

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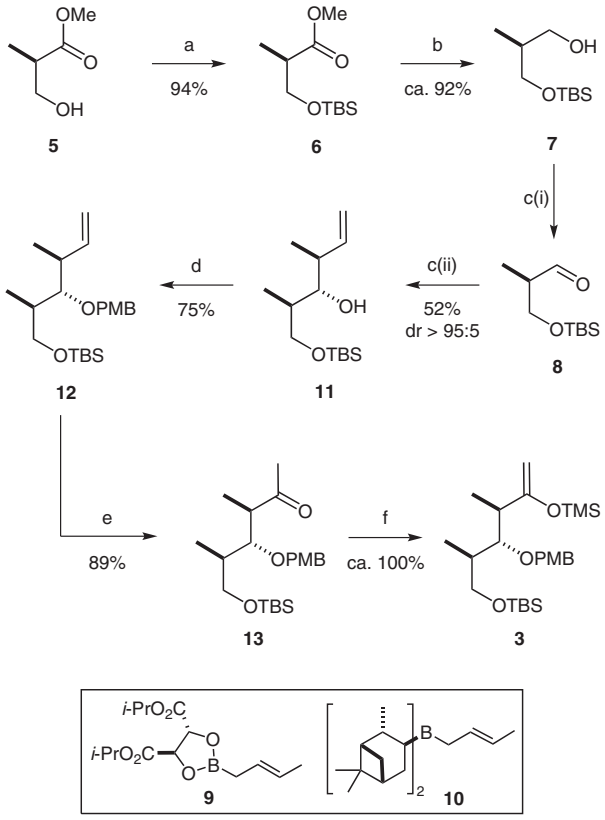


Scheme 2 *Reagents and conditions*: (a) TBSCl (1.0 equiv), imidazole (1.2 equiv), DMAP (10 mol%), CH_2Cl_2, 0 °C, 3 d, 94%; (b) DIBAL-H (2.5 equiv),CH_2Cl_2–toluene, –78 to –30 °C, 3.5 h, ca. 92%; (c) (1) $(COCl)_2$ (1.3 equiv), DMSO (2.6 equiv), Et_3N (6.5 equiv), CH_2Cl_2, –78 °C to r.t.; (2) **10**, THF, –78 °C; (3) NaOH, H_2O_2, –78 °C to r.t., 52%; (d) *p*-methoxybenzyl trichloroacetimidate (1.3 equiv), TfOH (0.3 mol%), CH_2Cl_2–cyclohexane (1:2), 0 °C to r.t., 18 h, 75%; (e) $PdCl_2$ (20 mol%), $Cu(OAc)_2 \cdot H_2O$ (2.0 equiv), O_2 (1 atm), *N*,*N*-dimethylacetamide–H_2O, r.t., 3 d, 89%; (f) LDA (2.6 equiv), TMSCl (6.6 equiv), THF, –78 °C to r.t., ca. 100%.

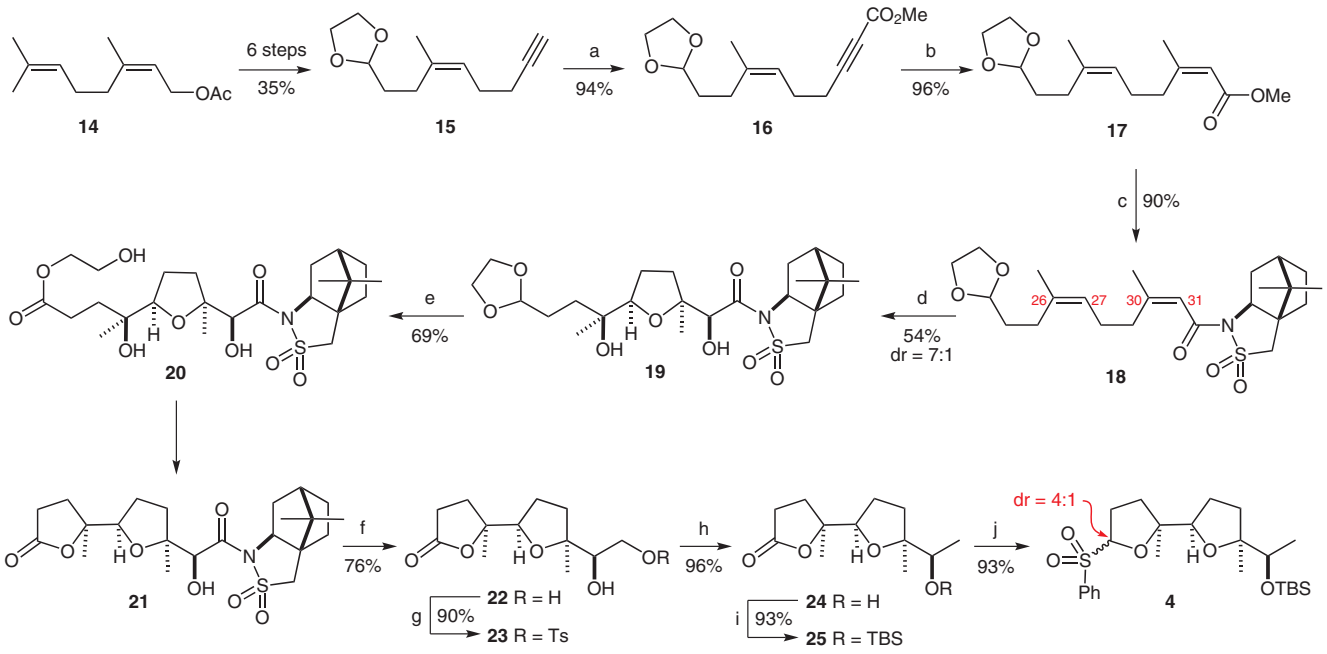
carboxylation of the terminal alkyne afforded the ynoate ester **16**, which then underwent *cis*-carbocupration to the α,β-unsaturated ester **17**.[18,19] High *Z*-stereoselectivity (*Z*/*E* >97:3) was observed provided the carbocupration reaction and the subsequent methanol quench were conducted below –70 °C in tetrahydrofuran rather than diethyl ether. The carboxylic acid derived from hydrolysis of methyl ester **17** was activated by reaction with the Ghosez reagent $[Me_2C{=}C(Cl)NMe_2]$[20,21] because more conventional reagents, such as oxalyl chloride, caused some premature destruction of the acetal even when the reaction was performed in the presence of base. The activated ester reacted with the sodium salt of (1*R*,2*S*)-camphor-10,2-sultam to give the desired diene fragment **18** in 90% overall yield from methyl ester **17**.

The key step in the sequence, the permanganate-mediated oxidative cyclisation of the diene **18** to the tetrahydrofuran diol **19**, was based on a precedent established by Walba[22] with many refinements and insights being provided recently by Brown and co-workers.[23–29] The reaction simply involved slow addition of an aqueous solution of potassium permanganate (2 equiv) and acetic acid (2.2 equiv) to a rapidly stirring solution of diene **18** in acetone containing pH 6 acetate buffer at –35 °C. The acetic acid was essential to neutralise the potassium hydroxide generated during the oxidation. The product was isolated in 54% yield as an inseparable 7:1 mixture of diastereoisomers in which the major component was the desired tetrahydrofuran diol **19**. Oxidation of the dioxolan function by exposure to ozone in ethyl acetate at low temperature afforded the intermediate ester **20**, which lactonised on exposure to a catalytic amount of *p*-toluenesulfonic acid (PTSA) to give the lactone **21** (mp 172–174 °C) as a single enantiomer in 69% overall yield from **19**.[30] Reductive cleavage of the sultam chiral auxiliary afforded the crystalline diol **22**, the structure and stereochemistry of which was established previously by Robinson and co-workers.[31]

To complete the sequence, the primary hydroxy group of diol **22** was selectively tosylated via the stannylene intermediate, and the resultant tosylate **23** was reduced via its iodoalkane derivative with tributyltin hydride. Protection of the remaining hydroxy group gave the crystalline TBS ether **25** in 80% overall yield from diol **22**. Finally, reduction of the lactone **25** gave a diastereoisomeric mixture of lactols that was treated with freshly prepared benzenesulfinic acid in the presence of calcium chloride as a dehydrating agent.[32] The desired sulfones **4** were obtained in 93% yield as an inseparable mixture of diastereoisomers (dr = 4:1).

The ozonolysis of dioxolan **19** deserves further comment. The scope and mechanism of the rapid and efficient oxidation of acetals with ozone were described in detail by Deslongchamps, Taillefer and co-workers.[33–38] They postulated the insertion of ozone into the acetal C–H bond to generate an intermediate hydrotrioxide such as **26** (Scheme 4), which decomposes to the hydroxyethyl ester **20** and singlet oxygen. In the case at hand, the oxidation of dioxolan **19** required careful monitoring because excess ozone caused an analogous secondary oxidation of the hydroxyethyl ester **20** to the lactone **29** presumably via the intermediate **27**.

The union of fragments **3** and **4** was accomplished by the procedure of Ley and co-workers (Scheme 5).[39] A mixture of enolsilane **3** and sulfone **4** in dichloromethane was added to a solution of $Et_3Al_2Cl_3$ (freshly prepared from equimolar quantities of Et_2AlCl and $EtAlCl_2$) in hexane at –78 °C. After warming to –30 °C, the reaction was quenched with aqueous ammonium chloride to give the diastereoisomeric α-heteroalkylation products **30** and **31** in 98% yield. The diastereoisomers were separable by column chromatography and easily quantified by integration of the ^1H NMR signals for the C22 methylene protons. The stereochemistry of the alkylation products could not be assigned with confidence at this stage, but subsequent conversion into the ionomycin intermediate **2** established that the minor diastereoisomer **31** had the correct configuration at C23. Precomplexation of the ketone **31** with $MeAlCl_2$ (5 equiv) in dichloromethane at –78 °C, followed by addition of tributyltin hydride (5 equiv), accom-



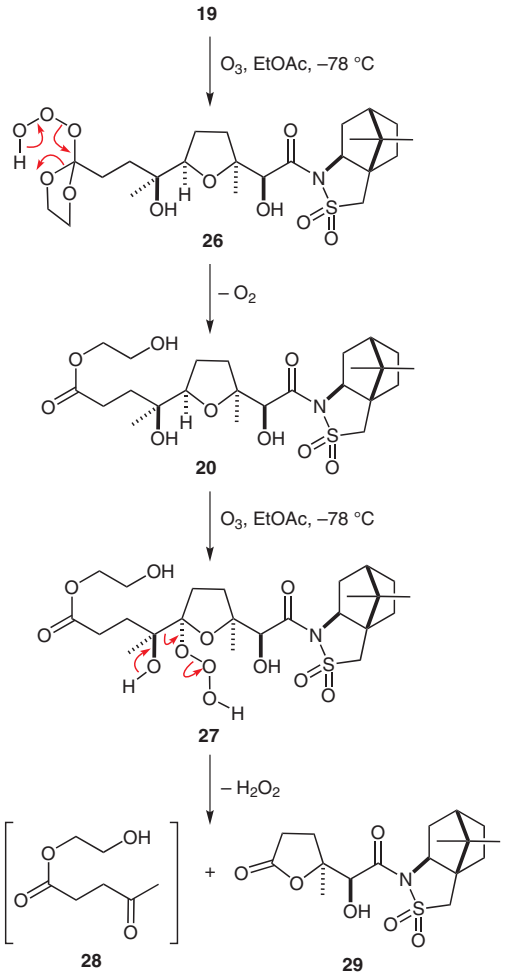
Scheme 3 *Reagents and conditions*: (a) (1) *n*-BuLi (1.1 equiv), THF, –78 to –5 °C; (2) $ClCO_2Me$ (2.0 equiv), THF, –90 °C, 94% (2 steps); (b) MeLi·LiBr (2.2 equiv), CuI (1.1 equiv), THF, –85 °C, 3 h, 96%; (c) (1) NaOH (5.5 equiv), $NaHCO_3$ (0.5 equiv), MeOH–H_2O, reflux, 2 h; (2) $Me_2C{=}C(Cl)NMe_2$ (1.25 equiv), Et_2O, 0 °C, 30 min; (3) sodium salt of (1*R*,2*S*)-camphor-10,2-sultam (1.0 equiv), toluene, r.t., 3.5 h, 90% (3 steps); (d) $KMnO_4$ (2.0 equiv), AcOH (2.2 equiv), pH 6 acetate buffer, acetone–H_2O, –35 °C, 5 h, 54% (dr = 7:1); (e) (1) O_3, EtOAc, –80 °C; (2) PTSA (cat.), CH_2Cl_2, r.t., 8 h, 69% (2 steps); (f) BH_3·SMe_2 (1.5 equiv), $NaBH_4$ (0.9 equiv), THF–toluene, –10 °C, 2 h, 76%; (g) (1) Bu_2SnO (1.2 equiv), benzene, reflux, 3 h; (2) TsCl (1.1 equiv), TBAB (0.5 equiv), r.t., 30 min, 90% (2 steps); (h) Bu_3SnH (1.0 equiv), NaI (2.5 equiv), 1,1′-azobis(cyclohexanecarbonitrile) (10 mol%), DME, 80 °C, 18 h, 96%; (i) TBSCl (1.2 equiv), Et_3N (1.2 equiv), DMAP (0.1 equiv), CH_2Cl_2, reflux, 3 d, 93%; (j) (1) DIBAL-H (1.2 equiv), toluene, –78 °C, 2 h; (2) $PhSO_2H$ (1.8 equiv), $CaCl_2$ (3.0 equiv), CH_2Cl_2, r.t., 18 h, 93%, dr = 4:1, (2 steps).

plished the simultaneous reduction of the ketone and deprotection of the PMB ether to give the *syn*-diol **32** in 62% yield.[40] Treatment of diol **32** with 2,2-dimethoxypropane and a catalytic amount of camphorsulfonic acid in acetone afforded a mixture of the fully protected acetonide **33** (53%) together with the target C17 alcohol **2** (35%). The *syn* stereochemistry of the acetonide was established from the ^{13}C NMR signals at δ = 19.4 and 30.3 ppm for the *gem*-dimethyl groups.[41] To complete the sequence, the primary TBS ether in **33** was selectively cleaved using HF·pyridine in tetrahydrofuran at room temperature to afford pure **2** in 72% yield. The structure and stereochemistry of **2** was identified by comparison of its ^1H and ^{13}C NMR spectra and $[\alpha]_D$ value with the data recorded on a sample of **2** prepared by a different route[5] and with the data reported by Hanessian and co-workers.[7]

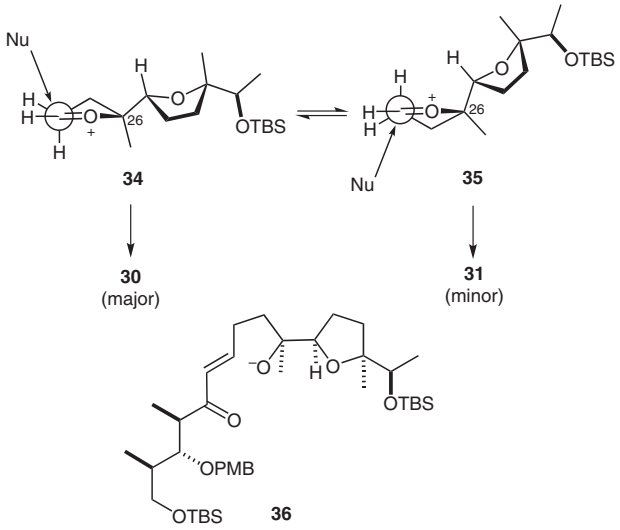
The adverse stereochemistry observed in the Ley α-heteroalkylaton reaction can be rationalised by the stereoelectronic model developed by Schmitt and Reissig[42–44] (Scheme 6) in which the reaction proceeds through a five-membered-ring oxocarbenium ion that may exist in two distinct envelope conformations (**34** and **35**) in rapid equilibrium. The major (undesired) isomer forms as a consequence of Felkin–Anh addition (i.e., 'inside' attack) of the enolsilane nucleophile on the more abundant conformer **34**, with the bulkier tetrahydrofuran substituent at C26 occupying the pseudoequatorial position. The minor (desired) isomer is derived from Felkin–Anh addition to the less abundant conformer **35**, with the tetrahydrofuran ring at C26 in a pseudoaxial position. A complementary model proposed by Woerpel and co-workers[45] posits that facial selectivity is a consequence of product development control. Thus 'inside' attack is favoured because rehybridization in the transition state during addition to the oxocarbenium ion leads to a staggered conformation with the adjacent methylene at C24, whereas 'outside' attack leads to a higher-energy, eclipsed conformation.

In an effort to improve the stereochemical outcome of the Ley α-heteroalkylation, we attempted to equilibrate ketones **30** and **31** through a base-catalysed β-elimination to the enone **36** (Scheme 6) followed by re-addition, but were unsuccessful; 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in refluxing benzene, or caesium carbonate in methanol did nothing, whereas application of sodium methoxide in methanol or potassium *tert*-butoxide in tetrahydrofuran destroyed the substrates. Other base–solvent combinations – with or without apotropaic chants – were equally fruitless and led to a change in strategy that was ultimately successful.[5]

In conclusion, intermediate **2**, harbouring nine of the fourteen stereogenic centres of ionomycin, has been synthesised. The first key step was the auxiliary-directed oxidative cyclisation of a diene to generate a tetrahydrofuran ring and four stereogenic centres in a single operation. Recent results by Brown and co-workers suggest that a similar oxidative cyclisation of a suitable triene sub-

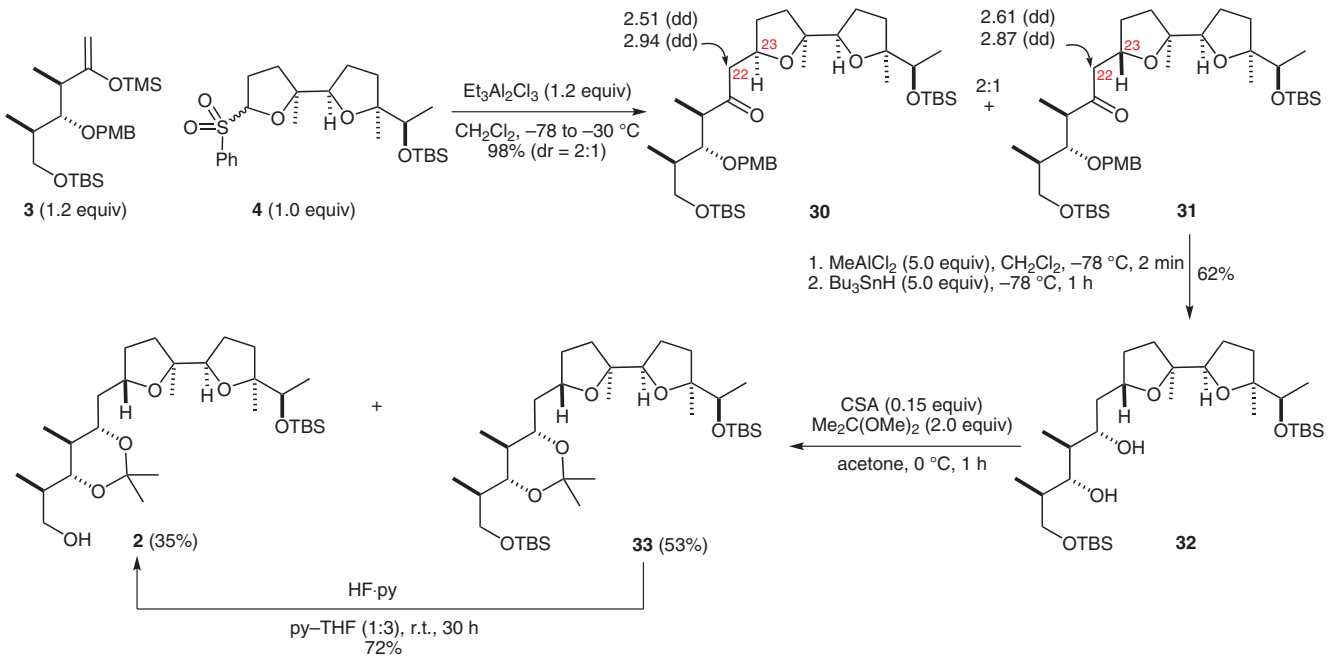


Scheme 4



Scheme 6

strate could deliver both tetrahydrofuran rings in a single operation.[46–48] Moreover, by using asymmetric phase-transfer catalysis, the asymmetric oxidative cyclisation could be accomplished without the need for a chiral auxiliary.[49] The second key step, the α-heteroalkylation of enolsilane **3**, has rarely been applied to the synthesis of substituted tetrahydrofurans.[39,50] In our hands the reaction was very efficient in terms of yield (99%), but the diastereoselectivity was modest (2:1) and favoured the unwanted diastereoisomer – a problem we were unable to fix.



Scheme 5

Supporting Information and Primary Data

Experimental details, ^{1}H and ^{13}C NMR spectra and their associated FIDs for compounds **2**, **3**, **4**, **11**, **12**, **13**, **17**, **18**, **21**, **22**, **23**, **24**, **25**, **29**, **30**, **31**, **32**, and **33** are available online free of charge at http://www.thieme-connect.com/ejournals/toc/synthesis. Primary data for this article can be cited using the following DOI: 10.4125/pd0007th.

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