COMMUNICATION

Total synthesis of the protein phosphatase inhibitor okadaic acid

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The total synthesis of the protein phosphatase inhibitor okadaic acid 1 is reported using a convergent coupling strategy of three components, all of which may be prepared using chemistry developed in our laboratories.

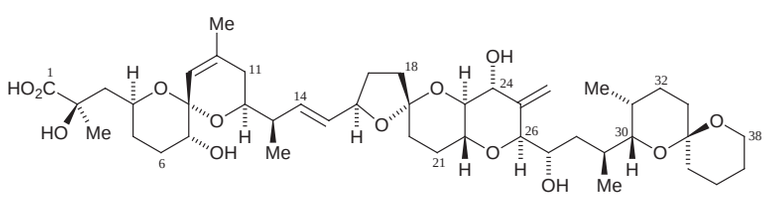
Okadaic acid **1** is a polyether, marine natural product produced by various species of dinoflagellate micro-algae, *e.g. Prorocentrum lima*.[1] These unicellular organisms frequently accumulate in sponges[2] such as *Halichondria okadai*, found along the Pacific coast of Japan, and *Halichondria melanodocia* which is of Caribbean origin. The various biological properties of okadaic acid have been extensively documented,[3] however it is the protein phosphatase inhibitory effect† which has attracted most attention, especially for the probing of biological mechanisms.[4] Okadaic acid has also stimulated interest from synthetic organic chemists and two total syntheses have been reported to date,[5] as well as approaches to various fragments of the natural product.[6] Here we describe a new total synthesis of okadaic acid **1** which highlights some of the chemistry developed in our laboratories.

Okadaic acid **1** represents a significant challenge for synthesis in that it contains not only seventeen stereogenic centres, but also a number of allylic oxygen substituents, three distinct types of double bond, three spiroketal units and a fully substituted α-hydroxy acid group. Our route to **1** proposes to bring together three fragments **2**, **3**, and **4** in a convergent fashion which, after appropriate modification, should lead to the natural product (Scheme 1).

For the preparation of the first component **2**, we make use of chemistry that was specifically developed for the asymmetric synthesis of α-hydroxy acids using chiral dispiroketals (Scheme 2).[7] Accordingly, glycolic acid was reacted with (*S*,*S*)-diphenylbis(dihydropyran) **5** in the presence of triphenylphosphine hydrobromide to give the crystalline dispiroketal **6** as a single, diastereoisomerically pure product. The selectivity arises from the strong preference for equatorial positioning of the phenyl groups and maximum operation of anomeric effects at the newly formed spiro-centres. Double alkylation of **6**, initially with methyl iodide and subsequently with allyl bromide, afforded the compound **7** in which the new stereogenic centre was that required for okadaic acid. This sequence proceeded well in 74% overall yield.

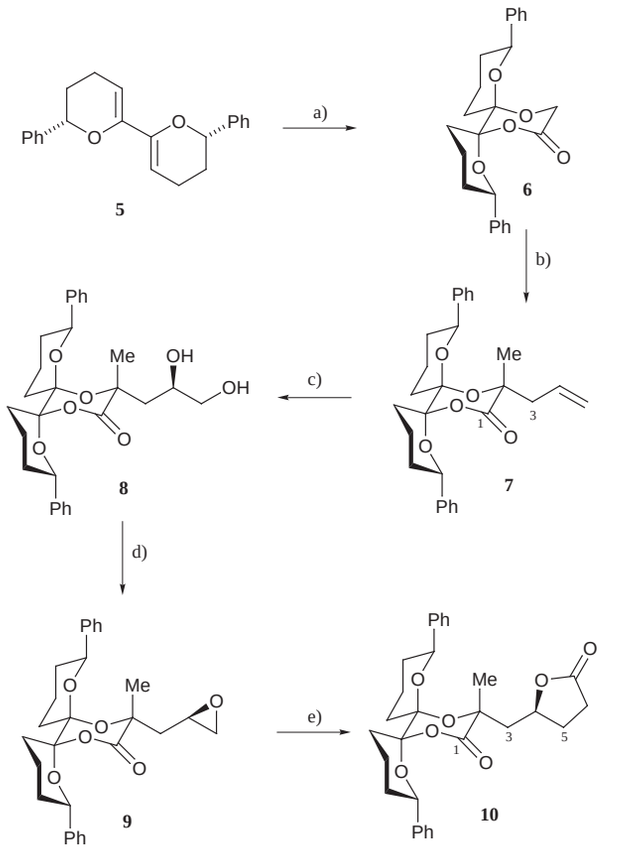
Elaboration of **7** to the lactone **10** was achieved by a straightforward sequence of reactions. Asymmetric dihydroxylation of **7** using the Sharpless $(DHQD)_2PYR$ ligand[8] proceeded in 82% yield giving the corresponding diol **8** with an 87% diastereoisomeric excess. Although the mixture of diastereoisomers could not be readily separated at this stage, reaction of **8** under the Sharpless–Kolb protocol[9] provided the epoxide **9** which was isolated as a single enantiomer. The epoxide was opened with a vinyl cuprate and the vinyl group subsequently hydroborated with $BH_3{\cdot}SMe_2$ using a buffered hydrogen peroxide work-up. Finally, oxidation with tetra-*n*-propylammonium perruthenate (TPAP)[10] afforded the lactone **10** in 31% overall yield from **7**. This lactone comprises the C1–C7 component necessary for formation of the first spiroketal fragment **2** (Scheme 2).

The remaining C8–C14 unit of **2** was derived from the pyranone **11**, prepared using well established Danishefsky chemistry (Scheme 3).[11] Addition of methyllithium to **11** in

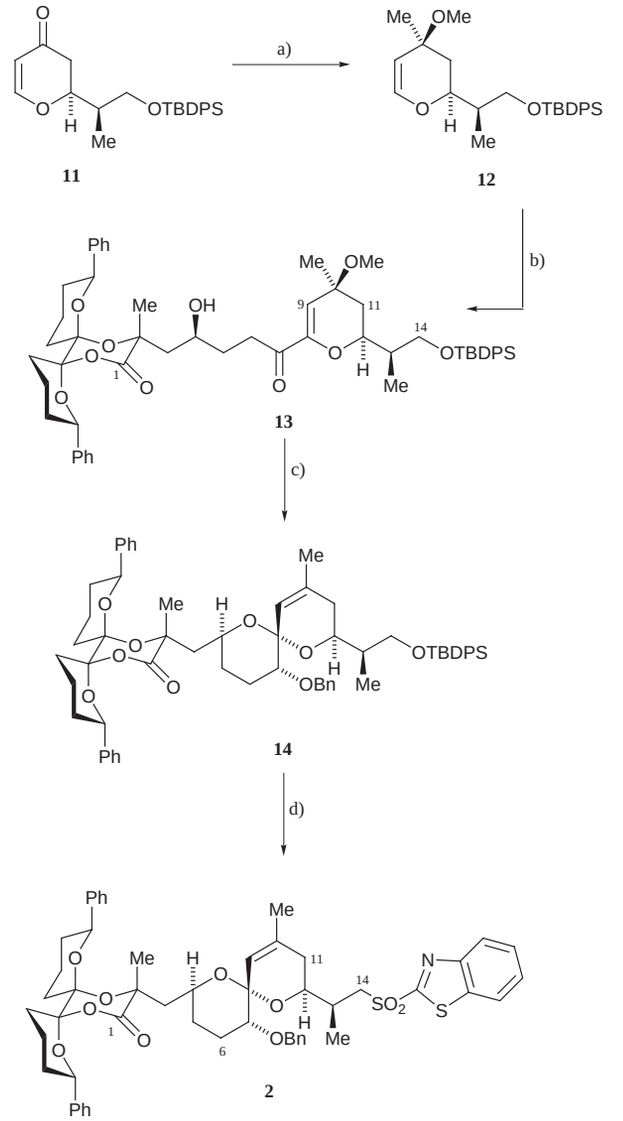


Okadaic Acid 1

Scheme 1



Scheme 2 *Reagents and conditions*: a) i) glycolic acid, $Ph_3P{\cdot}HBr$ (10 mol%), CH_2Cl_2, 89%; b) i) LDA, THF–PhMe–DMPU, −78 °C then BuLi, MeI, 87%; ii) LDA, THF–DME–DMPU, −78 °C then BuLi, allyl bromide, −78 °C to room temp., 95%; c) $K_2OsO_2(OH)_4$ (5 mol%), $(DHQD)_2PYR$ (5 mol%), $K_3Fe(CN)_6$, K_2CO_3, $Bu^tOH:H_2O$ (1:1), 0 °C, 82%; d) i) $(MeO)_3CCH_3$, PPTS, CH_2Cl_2; ii) AcBr, 80% (2 steps); iii) K_2CO_3, MeOH, 98%; e) i) BuLi, (vinyl)$SnBu_3$, CuCN, LiCl, THF, −78 °C then $BF_3{\cdot}OEt_2$, 70%; ii) $BH_3{\cdot}SMe_2$, THF then phosphate buffer (pH 7), H_2O_2, 87%; iii) TPAP (10 mol%), NMO, 4 Å sieves, CH_2Cl_2, 0 °C, 78%.



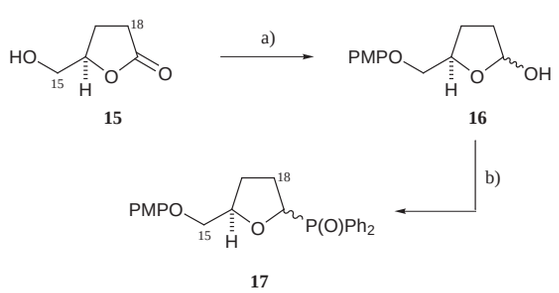
Scheme 3 *Reagents and conditions*: a) i) MeLi·LiBr, THF, −78 °C, 91%; ii) Ag_2O, MeI, ultrasound, 98%; b) i) $KOBu^t$, BuLi, THF, −78 °C then Bu_3SnCl; ii) MeLi, TMEDA, THF then **10**, −78 °C, 54% (2 steps); c) i) AcOH–H_2O–THF (3:1:1), 79%; ii) $NaBH_4$, EtOH, 0 °C, 90%; iii) NaH, BnBr, Bu_4NI (cat), 92%; d) i) TBAF, THF, 95%; ii) 2-sulfanylbenzothiazole, Ph_3P, DEAD, THF, −5 °C to room temp., 76%; iii) $Mo_7O_{24}(NH_4)_6{\cdot}4H_2O$, H_2O_2, EtOH–H_2O, 78%.

the presence of LiBr occurred, predominantly from the least hindered face, to give a readily separable 20:1 mixture of diastereoisomeric alcohols. *O*-Alkylation of the major diastereoisomer with MeI and Ag_2O using ultrasound—conditions first developed to alkylate similarly sensitive alcohols during our synthesis[12] of milbemycin β_1—provided the dihydropyran **12** in 86% overall yield from **11**. Deprotonation of **12** with Schlosser's base[13] and entrapment of the anion with tributyltin chloride, was followed by *trans*-metallation with MeLi and addition of the lactone **10** to give the acylated enol ether **13** in 54% yield. On treatment with mild acid, cyclisation occurred to give a spiroketal product which was reduced stereoselectively with $NaBH_4$ and benzylated under standard conditions, affording **14** in 65% overall yield. Finally, conversion to the sulfone **2** was achieved in 56% yield by deprotection with tetra-*n*-butylammonium fluoride (TBAF), displacement of the unmasked alcohol with 2-sulfanylbenzothiazole under Mitsunobu conditions and oxidation using $Mo_7O_{24}(NH_4)_6{\cdot}4H_2O$ (Scheme 3).[14]

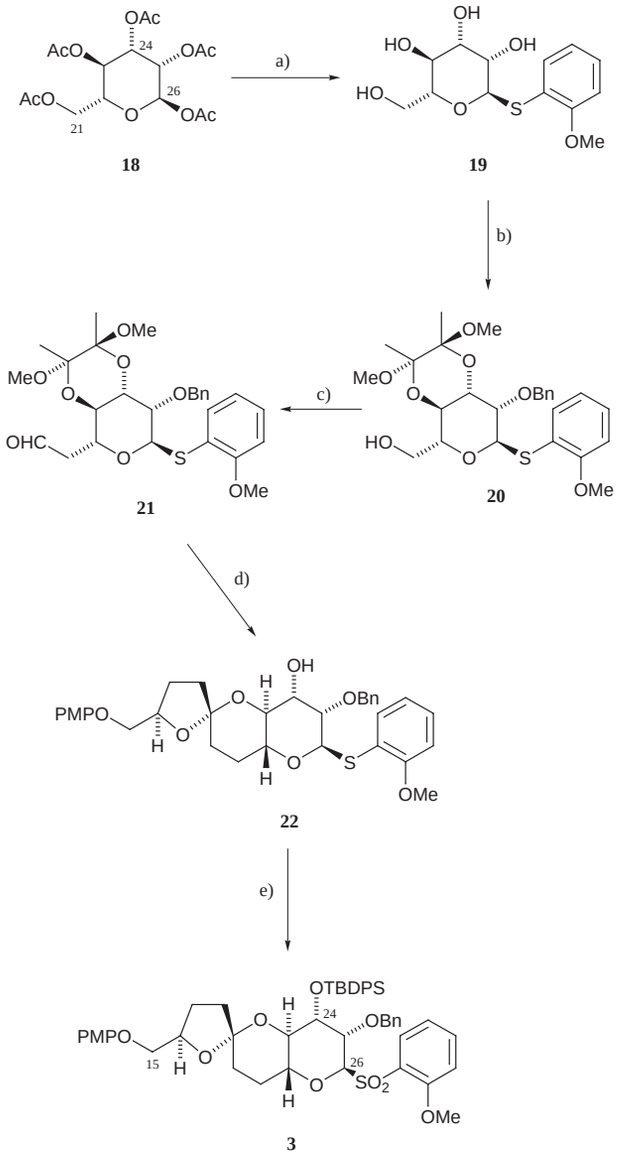
The choice of phenyl groups in the dispiroketal portion of this fragment was crucial in our synthesis design since not only do they direct the stereochemical outcome during alkylation, they also serve to facilitate later removal of the otherwise highly stable dispiroketal, *via* reductive cleavage of the benzylic carbon–oxygen bonds. Moreover, the benzothiazole unit in **2** was chosen in order to allow later coupling to afford the *E*-double bond required in **1**, using the excellent procedure developed by S. Julia.[15]

For the synthesis of the central fragment **3**, we designed a route which would also use some of the methods developed by our laboratories.

The commercially available hydroxylactone **15** was protected as its *p*-methoxyphenyl derivative using Mitsunobu conditions,[16] prior to reduction with diisobutylaluminium hydride (DIBAL-H) to give the lactol **16** in an overall yield of 82% (Scheme 4). The further transformations of **16** to afford the required diphenylphosphine oxide **17** were achieved in quantitative yield using a method we had developed earlier for



Scheme 4 *Reagents and conditions*: a) i) 4-methoxyphenol, Ph_3P, DEAD, THF, reflux, 84%; ii) DIBAL-H, PhMe, −78 °C, 98% (1:1 mixture of anomers); b) i) $Ph_3P{\cdot}HBr$, MeCN; ii) NaOH (aq), reflux, 100% (2 steps).



Scheme 5 *Reagents and conditions*: a) i) 2-methoxybenzenethiol, $BF_3{\cdot}OEt_2$, CH_2Cl_2, 87%; ii) K_2CO_3, MeOH, 100%; b) i) butane-2,3-dione, $(MeO)_3CH$, MeOH, CSA, reflux, 68%; ii) NaH, BnBr, DMF, 95%; c) i) Tf_2O, Et_3N, CH_2Cl_2, −78 °C; ii) NaCN, DMF–MeCN, 84% (2 steps); iii) DIBAL-H, PhMe, −78 °C, 90%; d) i) **18**, LDA, THF, −78 °C then **22** then $KOBu^t$, THF, −78 °C to room temp.; ii) TFA–H_2O–CH_2Cl_2 (9 : 1 : 30), 60% (2 steps); e) i) TBDPSCl, imidazole, DMF, 87%; ii) MCPBA, NaOAc, CH_2Cl_2, 0 °C, 96%.

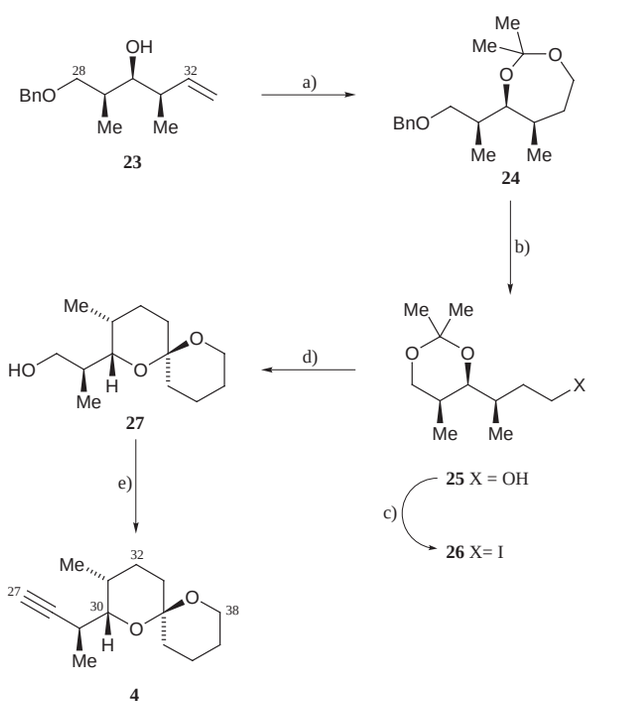
spiroketal synthesis.[17] This involved treatment with triphenylphosphine hydrobromide and alkaline hydrolysis of the resulting phosphonium salt with aqueous sodium hydroxide.

The remaining core of the central fragment **3** was constructed from an inexpensive source which contains the majority of the required stereogenic centres, namely α-D-mannose pentaacetate **18**. This was reacted with 2-methoxybenzenethiol in the presence of $BF_3{\cdot}OEt_2$, then deacetylated under Zemplèn conditions[18] to give the tetrol **19** in 87% yield. The incorporation of the sulfide functionality would allow us to readily activate the anomeric centre to nucleophilic displacement, by oxidation to the corresponding sulfone, at a later stage in the synthesis.

The diequatorial diol component of the tetraol **19** was selectively protected with butane-2,3-dione to give the corresponding butane 2,3-diacetal (BDA) derivative using a method first reported by our group.[19] Interestingly, subsequent monobenzylation using standard conditions occurred on the remaining secondary hydroxy group, in preference to protection of the primary C21 alcohol, providing **20** in 65% yield over the two steps. The protected derivative **20** was then elaborated to the aldehyde **21** using relatively standard conditions; triflation, cyanide displacement and finally DIBAL-H reduction of the nitrile, giving **21** in 76% overall yield (Scheme 5).

The spiroketal **22** was assembled using conditions derived from our experience with related systems[17] and our knowledge of the reactivity of the BDA functionality towards acids.[19] Accordingly, the diphenylphosphine oxide **17** was deprotonated with LDA at −78 °C and reacted with the aldehyde **21**. Treatment of the initially formed adduct with potassium *tert*-butoxide promoted elimination to an enol ether which was then subjected, without purification, to an aqueous solution of trifluoroacetic acid. This resulted in removal of the BDA group, protonation of the enol ether and concomitant spiroketalisation to afford **22** in 60% overall yield. Finally, **22** was converted to **3** in 84% yield by protection of the free hydroxy group as its *tert*-butyldiphenylsilyl ether and oxidation of the sulfide using *m*-chloroperbenzoic acid (MCPBA) (Scheme 5).

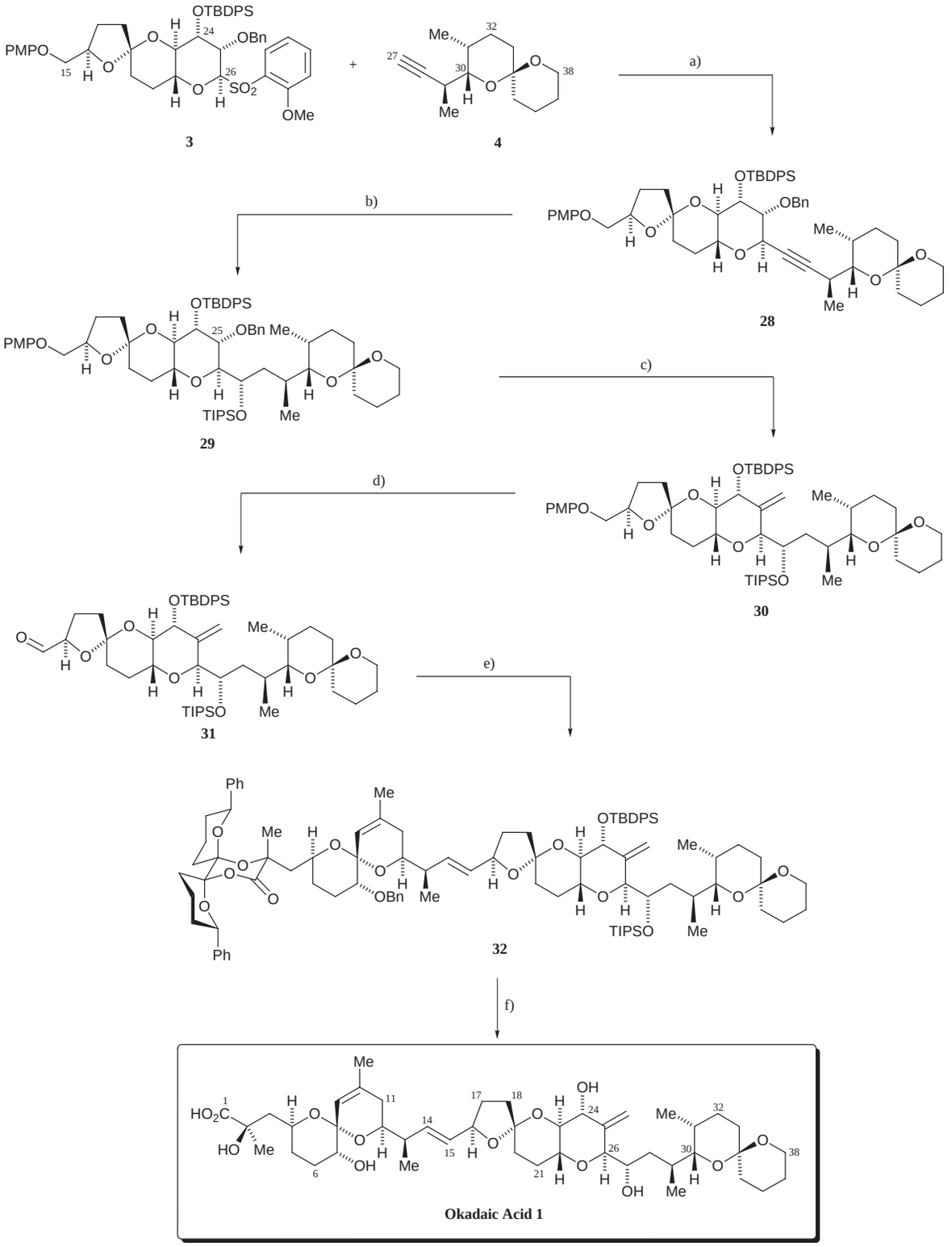
The preparation of the final spiroketal fragment **4** commences with the known protected diol unit **23**, which may be accessed using the efficient route developed by Brown[20] (Scheme 6).



Scheme 6 *Reagents and conditions*: a) i) 9-BBN, THF, 65 °C then NaOH (aq), H_2O_2, 0 °C to room temp., 95%; ii) 2-methoxypropene, PPTS, CH_2Cl_2, 96%; b) i) Na, NH_3 (l), Et_2O; ii) PPTS, CH_2Cl_2, 89% (2 steps); c) i) MsCl, NEt_3, CH_2Cl_2, −5 °C; ii) NaI, butan-2-one, 4 Å sieves, 45 °C, 98%; d) i) 2-(phenylsulfonyl)tetrahydropyran, BuLi, THF–DMPU, −78 °C then **27**; ii) CSA (cat.), MeOH, 90% (2 steps); e) i) TPAP, NMO, 4 Å sieves, CH_2Cl_2; ii) Ph_3P, CBr_4, 0 °C, 70% (2 steps); iii) BuLi, 100%.

Hydroboration of **23** using 9-BBN with a basic peroxide work-up and subsequent acetal protection of the diol gave the seven membered isopropylidene ring derivative **24** in 91% yield. Reductive removal of the benzyl protecting group followed by treatment with pyridinium tosylate (PPTS), induced the isomerisation[21] of the seven membered ring to the more thermodynamically stable six membered ring acetal **25** in 89% yield. The free alcohol was then converted to the iodide **26** by routine methods.

For the formation of the fragment **4** we make use of an alternative route to spiroketals which was also devised within our laboratories.[22] Thus, reaction of the anion generated from 2-(phenylsulfonyl)tetrahydropyran using *n*-butyllithium, with the iodide **26**, followed by treatment with methanolic camphorsulfonic acid produced the spiroketal **27** in an excellent 90% yield. This process involves a cascade of reactions after the



Scheme 7 *Reagents and conditions*: a) i) **4**, BuLi, PhMe, 0 °C then Me_2AlCl, CH_2Cl_2, 0 °C to room temp. then **3**, 70%; b) i) 9-BBN, THF, reflux then NaOH (aq), H_2O_2, room temp.; ii) $NaBH_4$, EtOH, 0 °C, 67% (2 steps); iii) TIPSOTf, 2,6-lutidine, CH_2Cl_2, 95%; c) i) H_2, Pd/C, MeOH–CH_2Cl_2, 95%; ii) TPAP, NMO, 4 Å sieves, CH_2Cl_2, 97%; iii) Cp_2TiMe_2, PhMe, reflux, 90%; d) i) CAN, MeCN–THF–H_2O (4 : 2 : 1), 0 °C, 98%; ii) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C then Et_3N, 90%; e) **2**, NHMDS, DMF–THF, −60 °C then **32**, −60 °C to room temp., 66%; f) i) TBAF, THF, 90%; ii) Ca, NH_3 (l), Et_2O, −33 °C, 30%.

initial alkylation; spontaneous antiperiplanar elimination of sulfinic acid was followed by deprotection of the isopropylidene acetal, protonation of the enol ether intermediate and spirocyclisation on acidification. The synthesis was completed by TPAP oxidation[10] of **27** to an intermediate aldehyde, which was converted to the acetylenic coupling partner **4** in 70% overall yield using the Corey–Fuchs procedure[23] (Scheme 6).

With all the fragments now in hand we investigated our proposed coupling strategy to complete the synthesis of the natural product.

Firstly we studied the union of the central sulfone portion **3** with the right hand acetylene fragment **4** (Scheme 7). Pleasingly, we found that after deprotonation of **4** with *n*-butyllithium and *trans*-metallation with dimethylaluminium chloride, addition of the sulfone gave the desired product **28** in 70% yield. This coupling represents a significant advance on the methodology

that we established for simple pyranyl and related sulfones.[24] We believe the presence of the *ortho*-methoxy group on the sulfone aryl ring greatly enhances the chelating ability on addition of the Lewis acidic reagent, thus increasing the sulfone reactivity and considerably improving the nucleophilic displacement reaction. Regioselective oxygenation of the propargylic ether **28** was achieved by hydroboration with 9-BBN using a basic peroxide work-up to afford a single ketone product, as anticipated on mechanistic grounds. This was stereoselectively reduced with sodium borohydride and the resulting alcohol immediately protected as the corresponding triisopropylsilyl ether **29**. These reactions proceeded smoothly to furnish **29** in 64% yield over the three steps (Scheme 7).

Next, the installation of the *exo*-methylene unit was carried out by elaboration of the C25 alcohol. Accordingly, removal of the benzyl group by hydrogenolysis, followed by TPAP oxidation[10] and reaction of the crude ketone with the Petasis reagent[25] at 100 °C, gave **30** in 83% overall yield. This compound was then readily converted to the aldehyde **31**, suitable for coupling with the left-hand fragment **2**, by clean oxidative cleavage of the *p*-methoxyphenyl ether and Swern oxidation in 88% yield (Scheme 7).

The final coupling involved deprotonation of **2** with sodium hexamethyldisilazide (NHMDS) and reaction of the stabilised anion with the aldehyde **31** under conditions first developed by Charette,[26] to afford the (*E*)-alkene **32** as the major product in 66% yield. A small quantity of the corresponding (*Z*)-isomer was also detected by 600 MHz ^{1}H NMR spectroscopy of the crude reaction mixture, but this was removed in the subsequent steps. Cleavage of the two silyl ether protecting groups in **32** proceeded uneventfully using TBAF. Finally, removal of both the remaining benzyl group and the diphenyldispiroketal was achieved in an unoptimised 30% yield by treatment with calcium metal in refluxing ammonia[27] for 30 minutes to give okadaic acid **1**, identical to an authentic sample[28] of the natural product (Scheme 7).

In summary, we have accomplished a new total synthesis of the protein phosphatase inhibitor okadaic acid **1** using some of the methods developed in these laboratories.

Acknowledgements

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Notes and references

† Okadaic acid is a highly potent and specific inhibitor of PP-1 and PP-2A.

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28 Authentic okadaic acid was kindly provided by Professor K. Yamada and Professor D. Uemura. Comparison between the synthetic and authentic compounds was made by superposition of the corresponding 600 MHz ^{1}H NMR spectra, co-elution by thin layer chromatography and electrospray accurate mass spectrometry.

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