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Bicyclic analogues of inositol 1,4,5-trisphosphate based upon adenophostin A

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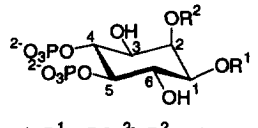
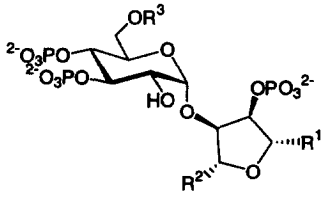
Abstract: The synthesis from *myo*-inositol of two bicyclic fused ring analogues of 1D-*myo*-inositol 1,4,5-trisphosphate in optically active form is described. The route demonstrates the application of the recently described butane-2,3-diacetal (BDA) protecting group to inositol chemistry, and features a novel construction of a dioxabicyclo[5.4.0] system using 3-chloro-2-chloromethyl-1-propene.

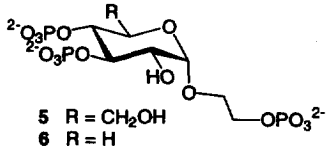
1D-*myo*-inositol 1,4,5-trisphosphate [Ins(1,4,5)P_3, **1**] is an intracellular signalling molecule that increases cytosolic Ca^{2+} concentrations in stimulated cells by activating Ins(1,4,5)P_3-gated Ca^{2+} channels [Ins(1,4,5)P_3 receptors, Ins(1,4,5)P_3Rs][1]. Structure-activity investigations[2] have established that although high-affinity Ins(1,4,5)P_3R ligands must contain an equivalent to the vicinal 4*R*,5*R*-*trans*-diequatorial bisphosphate and adjacent 6-hydroxyl group of Ins(1,4,5)P_3, slight variations in the positioning of the third (non-vicinal) phosphate group are tolerated, so that Ins(2,4,5)P_3 (**2**) for example, is recognised by the Ins(1,4,5)P_3R, albeit with 25-fold reduced affinity.[3] Surprisingly, the naturally occurring fungal metabolites adenophostins A (**3**) and B (**4**)[4] in which the non-vicinal phosphate is located on a separate ring from the vicinal pair have been found to bind to the Ins(1,4,5)P_3R with affinities 10 to 100-fold higher than Ins(1,4,5)P_3 itself and to release Ca^{2+} with



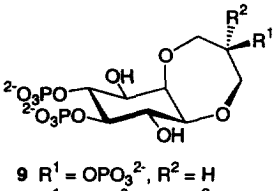
1 $R^1 = PO_3^{2-}$, R^2 = H
2 R^1 = H, $R^2 = PO_3^{2-}$



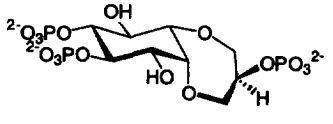
3 R^1 = adenine, $R^2 = CH_2OH$, R^3 = H
4 R^1 = adenine, $R^2 = CH_2OH$, R^3 = Ac
7 $R^1 = OCH_3$, $R^2 = CH_2OH$, R^3 = H
8 $R^1 = R^2 = R^3$ = H



5 $R = CH_2OH$
6 R = H



9 $R^1 = OPO_3^{2-}$, R^2 = H
10 R^1 = H, $R^2 = OPO_3^{2-}$



10 (alternative representation)

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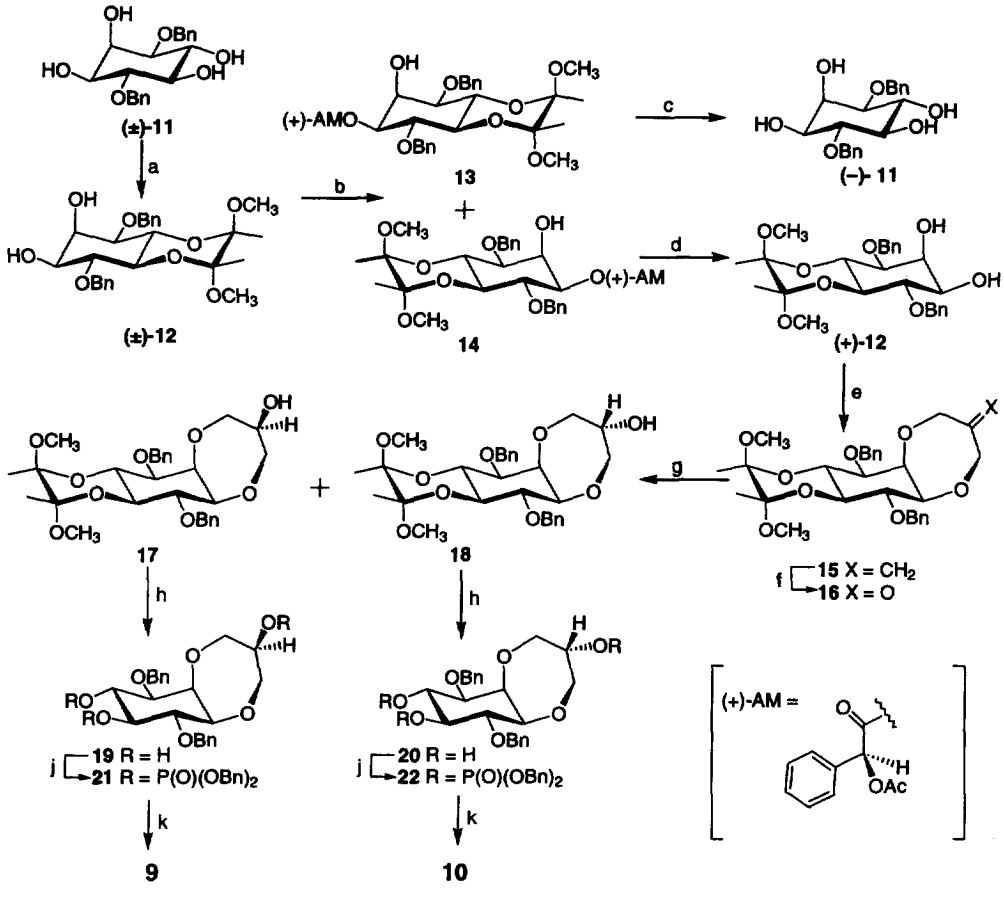
correspondingly high potency. A molecular modelling study[5] found that in adenophostin A, the non-vicinal phosphate group may be constrained by the ribose ring to a position slightly more extended than the 1-phosphate of Ins(1,4,5)P_3, and it has been suggested[4–6] that it is the precise positioning of this phosphate group that may account for the enhanced affinity of the adenophostins for the Ins(1,4,5)P_3R.

We and other groups have synthesised various carbohydrate-based Ins(1,4,5)P_3R ligands related to the adenophostins but lacking the adenine, including **5**[5,7] and **6**,[8] which were approximately 10-fold less potent than Ins(1,4,5)P_3 in Ca^{2+} release, and more recently **7**[9] and **8**,[10] which showed potencies similar to that of Ins(1,4,5)P_3. The finding that none of these ligands has shown significantly higher activity than Ins(1,4,5)P_3 may point to a specific role for the adenine component of the adenophostins, but it is also possible that they do not constrain the non-vicinal phosphate group in the appropriate position for optimal binding.[11] The latter possibility may be explored by the synthesis and biological evaluation of conformationally restricted analogues. As a first step in this direction, we have designed two bicyclic Ins(1,4,5)P_3 analogues **9** and **10**, in which the non-vicinal phosphate group is placed further away from the inositol ring than the 1-phosphate of Ins(1,4,5)P_3 and constrained in one of two distinct positions. These epimers may be regarded not only as related to Ins(1,4,5)P_3 and Ins(2,4,5)P_3, but also as first-generation conformationally restricted analogues of the adenophostins, designed to explore the potential interplay between fixing of the non-vicinal phosphate group and hydrophobic interactions of the adenine with the receptor. Molecular modelling of these analogues suggests that the non-vicinal phosphate in **10** is held in a position closer to that found in low energy conformations of the adenophostins than the equivalent phosphate in **9**, and therefore that epimer **10** should be the more potent of the two. We report here a synthetic route to **9** and **10**.

The route begins with the known DL-1,4-di-*O*-benzyl-*myo*-inositol **[(±)-11]**, readily accessible in 5 steps from *myo*-inositol.[12] The molecule contains two pairs of vicinal hydroxyl groups, and selective protection of the *trans*-vicinal pair was achieved using the recently described butane-2,3-diacetal (BDA) protecting group.[13] The modified procedure of Hense *et al.*[14] was employed, which uses 2,3-butanedione in place of 2,2,3,3-tetramethoxybutane. Thus, acid-catalysed reaction of (±)-**11** with 2,3-butanedione in refluxing methanol in the presence of trimethyl orthoformate as dehydrating agent gave the crystalline racemic diol (±)-**12**.[15] Regioselective DCC-promoted esterification of the equatorial hydroxyl group of (±)-**12** with (+)-(*S*)-acetylmandelic acid[16] gave two diastereoisomeric esters, which were separated by flash chromatography followed by recrystallisation to give pure **13** and **14**.[17] The absolute configuration of the more polar ester was determined by converting it into the known (–)-1D-1,4-di-*O*-benzyl *myo*-inositol **[(–)-11]**,[16] identifying this ester as **13** and the less polar ester as **14**. Saponification of **14** then gave the chiral diol (+)-**12** with the desired absolute configuration.



Reagents and conditions: a) 2,3-butanedione, MeOH, $CH(OMe)_3$, (±)-10-camphorsulphonic acid, reflux, 80%; b) (*S*)-(+)-acetylmandelic acid, DCC, DMAP, CH_2Cl_2, –20 °C to rt, 34% (**13**), 36% (**14**); c) (i) NaOH, MeOH, reflux; (ii) $CH_2Cl_2/CF_3COOH/H_2O$ 25:24:1, 93%; d) NaOH, MeOH, reflux, 95%; e) NaH, 3-chloro-2-chloromethyl-1-propene, DMF, 84%; f) $RuCl_3$, $NaIO_4$, $EtOAc/CH_3CN/H_2O$, 82%; g) $NaBH_4$, MeOH, 0 °C to rt, 21% (**17**), 67% (**18**); h) $CH_2Cl_2/CF_3COOH/H_2O$ 25:24:1, 83–84%; j) $(BnO)_2PNPr^i_2$, 1*H*-tetrazole, CH_2Cl_2; ii) *m*-CPBA, –78 °C to rt, 82–90%; k) H_2, 50 p.s.i., Pd–C, MeOH, 89–90%. Bn = benzyl.
The 1D-*myo*-inositol configuration is shown for racemic compounds (±)-**11** and (±)-**12**.

The required seven-membered ring was introduced by reaction of (+)-**12** with sodium hydride and 3-chloro-2-chloromethyl-1-propene (methallyl dichloride) in DMF to give **15**. Flash dihydroxylation[18] of the exocyclic alkene employing $RuCl_3/NaIO_4$ gave an inseparable 3:1 mixture of epimeric diols within 4 min, and prolongation of the reaction time to 1.5 h gave the tricyclic ketone **16**. Reduction of **16** with $NaBH_4$ in MeOH gave two epimeric products in a ratio of approximately 1 to 3. These alcohols were separated by flash chromatography and were isolated as crystalline solids. A single crystal X-ray study of the more polar alcohol (major product) showed it to be **18**, identifying the minor product as the epimer **17**.[19] The BDA protecting groups of **17** and **18** were cleaved using aqueous trifluoroacetic acid in dichloromethane to give triols **19** and **20**.

To the best of our knowledge, this is the first construction of a dioxabicyclo[5.4.0] system using methallyl dichloride. Phosphitylation of **19** and of **20** using bis(benzyloxy)(*N*,*N*-diisopropylamino)phosphine and 1*H*-tetrazole, followed by *in situ* oxidation with *m*-CPBA gave the trisphosphate triesters **21** and **22**. Finally, removal of all benzyl protecting groups by catalytic hydrogenation with Pd–C in MeOH gave the epimeric trisphosphates **9** and **10**, isolated as their triethylammonium salts after purification by ion exchange chromatography on Q-Sepharose Fast Flow and accurate quantification by total phosphate assay.

In conclusion, we have described syntheses of the first bicyclic analogues of Ins(1,4,5)P_3 designed to explore the structural basis for the potent activity of the adenophostins. Biological evaluation of **9** and **10** is in progress and full details will be reported elsewhere.

Acknowledgement

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19. **17**: mp 126–127 °C (hexane); R_f 0.20 ($CHCl_3$/acetone 10:1); $[\alpha]_D^{25}$ +33 (*c* 1, $CHCl_3$); **18**: mp 165–167 °C (EtOAc/hexane); R_f 0.12 ($CHCl_3$/acetone 10:1); $[\alpha]_D^{25}$ +29 (*c* 1, $CHCl_3$). We thank Dr M.F. Mahon for the X-ray crystal structure of **18**; full details will be reported elsewhere.