Exploration of ω-side chain addition strategies for the syntheses of isocarbacyclin and 15*R*-16-(*m*-tolyl)-17,18,19,20-tetranorisocarbacyclin†‡

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We describe alternative access to prostacyclin analogues by means of two ω-side chain addition strategies: Grignard reagent addition to an α,β-unsaturated Weinreb amide, followed by diastereoselective reduction of the corresponding enone system, and implementation of Seebach's alkylation chemistry. These strategies have led to the syntheses of biologically active prostacyclin analogues isocarbacyclin and 15*R*-16-(*m*-tolyl)-17,18,19,20-tetranorisocarbacyclin (15*R*-TIC), with modest to excellent diastereoselectivity.

Introduction

Discovered in 1976, prostacyclin (PGI_2),[1] (**1**), has shown diverse biological activity ranging from being a potent vasodilator and inhibitor of blood platelet aggregation to playing an important role not only in the peripheral organs but also in the central nervous system (CNS).[2] Unfortunately, due to its chemical and metabolic instability, resulting from the extremely labile nature of the vinyl ether moiety to hydrolysis ($t_{1/2}$ = 5 min at pH 7.4), clinical applications have been severly hampered. This instability has stimulated efforts towards the design and development of various analogues (Fig. 1) with the aim of chemical and metabolic stability combined with physiological activity.

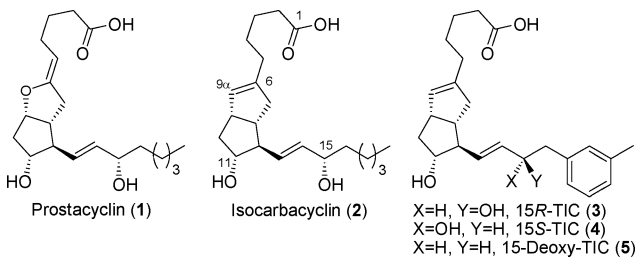
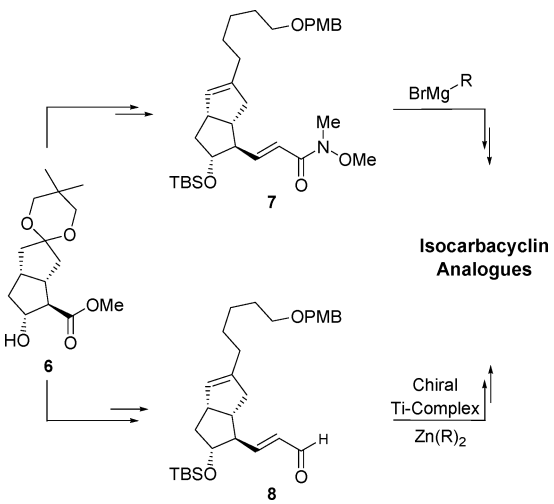


Fig. 1 Prostacyclin, isocarbacyclin and selected TIC derivatives.

Isocarbacyclin (**2**)[3] is one such potent analogue, which has shown promising application as a therapeutically useful agent.[4] 15*R*-16-(*m*-Tolyl)-17,18,19,20-tetranorisocarbacyclin **3** (15*R*-TIC),[5] a modified isocarbacyclin analogue has been used to visualise the specific location of the IP_2 receptor, a sub-type of the prostacyclin (PGI_2) receptor,[2] for both *in vitro* and *in vivo*[6] systems by autoradiography of rat brain slices and positron emission tomography (PET),[6,7] of a living rhesus monkey.[8] This CNS specific PGI_2 ligand and its 15-deoxy-TIC (**5**) counterpart,[9] both have exhibited an inhibitory effect on apoptosis of neuronal cells induced by a high oxygen (50%) atmosphere.[10] The most challenging aspects associated with the syntheses of isocarbacylcin and its analogues is the construction of the C6–C9α *endo*-cyclic double bond and the flexible introduction of the ω-side chain allowing for a wider range of analogues to be prepared. Through such a diversity orientated synthetic strategy, an array of isocarbacyclin analogues could be obtained, allowing their biological activity to be investigated further.



Scheme 1 Diverse orientated isocarbacyclin analogue synthesis.

The focus of our research has been to develop a strategy which would allow a large number of isocarbacyclin analogues to be synthesized, from a common synthetic intermediate, with only a minimum of synthetic steps. Typically, the ω-side chain for isocarbacyclin analogues is introduced *via* an (*E*)-selective Horner–Wadsworth–Emmons olefination reaction (C13–C14), where the yield varies from substrate to substrate,[11] followed by diastereoselective reduction of the C15 carbonyl functionality under reagent control. To maximise diversity, it was envisaged that *via* the addition of a suitable Grignard reagent to α,β-unsaturated Weinreb amide building block **7** (available from methyl ester **6**)[9b]

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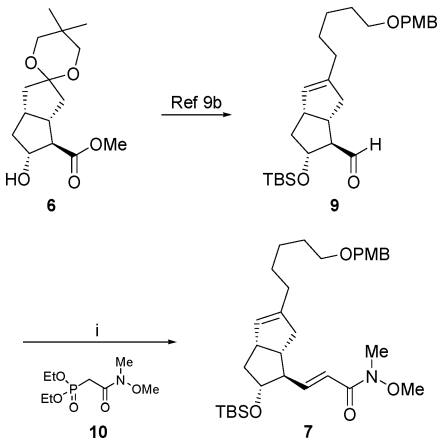
‡ Dedicated to Professor Manfred Christl on the occasion of his 65th birthday.

and subsequent diastereoselective reduction of the resulting enone, a direct and reliable access to the carbon skeletons of a number of isocarbacyclin analogues could be achieved. Alternatively, by invoking Seebach's alkylation method,[12] with α,β-unsaturated aldehyde **8**, we also believe that a high d.e. for the C15 hydroxyl group for a variety of functionalised isocarbacyclin analogues could be accessed (Scheme 1).[13]

Results and discussion

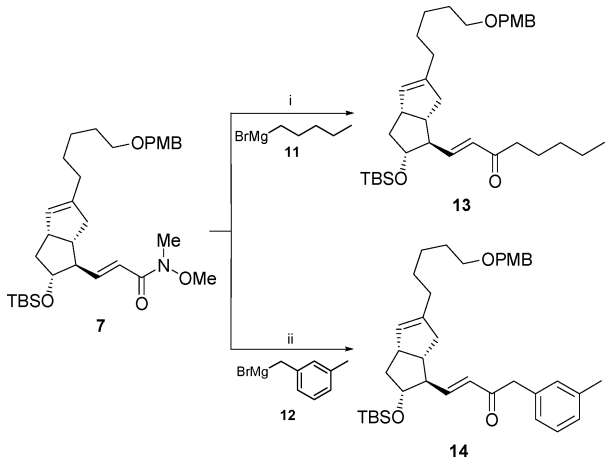
Known aldehyde **9**,[9b] was subjected to a Horner–Wadsworth–Emmons olefination reaction, with Weinreb amide phosphonate **10** which delivered α,β-unsaturated Weinreb amide **7** in excellent yield. Weinreb amide **7**, containing the common C1–C15 carbon skeleton of isocarbacyclin analogues, should act as a suitable building block for the preparation of isocarbacyclin (**2**) and its 15*R*-TIC (**3**) analogue (Scheme 2).



Scheme 2 Synthesis of Weinreb amide. *Reagents and conditions*: (i) NaH, **10**, THF, 0 °C, 87%.

Slow addition of either *n*-pentyl magnesium bromide **11**, or (3-methylbenzyl)magnesium bromide **12** (3 equiv.), at −78 °C, to Weinreb amide **7** delivered the corresponding enones **13** and **14** with yields of 94% and 90% respectively (Scheme 3).[14]

(*R*)-Me–CBS reduction of enone **13** was carried out according to Snapper *et al.*[15] which delivered the corresponding (*S*)-allylic alcohol with a d.r. of 9 : 1 (Scheme 4, Table 1). Similarly, enone **14** underwent reduction with (*S*)-Me–CBS to give the unnatural (*R*)-configured C15 hydroxy group, albeit with a modest diastereoselectivity (d.r. 6 : 1). Application of both the (*R*)- and (*S*)-*n*-Bu–CBS reagents to enones **13** and **14** respectively, which have been documented to give, in many cases, better selectivity



Scheme 3 Grignard reagent addition to Weinreb amide. *Reagents and conditions*: (i) 3 equiv. **11**, THF, −78 °C → 0 °C, 94%; (ii) 3 equiv. **12**, −78 °C → 0 °C, 90%.

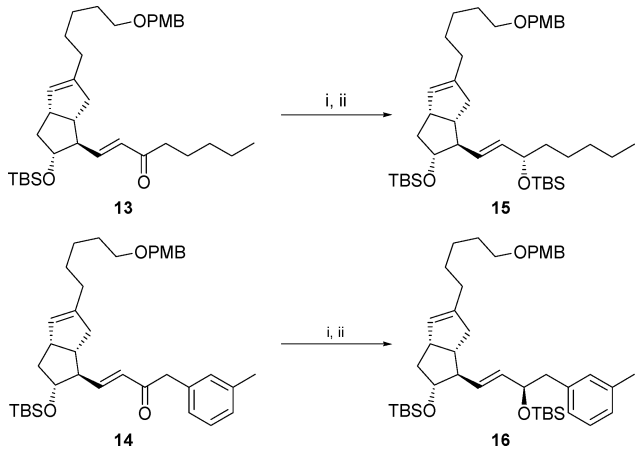
failed to do so in our case, showing only a slight increase in d.r. for both **13** and **14**. Switching the method of reduction to Noyori's BINAL-H reducing agent,[16] proved useful, although capricious, without the aid of a stock solution of the reducing agent. Enone **13** when treated with (*S*)-BINAL-H, at −100 °C for 2 hours, gave an impressive d.r. of over 35 : 1 (>94% d.e.). However, enone **14**, when treated with (*R*)-BINAL-H, also at −100 °C, delivered only a slightly improved d.r. of 8 : 1 compared to that obtained with the CBS reagents (d.r. 7 : 1). It has been documented in the literature that these enone systems and especially those leading to the unnatural (*R*)-C15 configuration have led to a mismatched case for the reduction.[17] The allylic alcohols,[18] resulting from enone reductions, were both protected as the TBS ethers, to deliver **15** and **16** (Scheme 4).

Although this Grignard reagent addition and subsequent reduction strategy proved to be synthetically useful, the limiting factor was the capricious diastereoselective reduction of the enone moiety; resulting in the need for either column chromatography or HPLC separation. Taking this under advisement, we thought that we could instead form the C15–C16 bond and set the C15 stereochemistry in one reaction by taking advantage of Seebach's alkylation method; the addition of a suitable dialkyl zinc reagent to an α,β-unsaturated aldehyde catalysed by a Ti–TADDOL complex. Reduction of Weinreb amide **7** with DIBAL-H at −78 °C delivered the corresponding α,β-unsaturated aldehyde **8**. Addition of dipentyl zinc **20**[19] to aldehyde **8**, in the presence of spirotitanate **17**, proceeded in a diasteroselective manner to give its corresponding allylic alcohol **21** with a d.r. of over 30 : 1

Table 1 Diastereoselective reduction of enones **13** and **14**

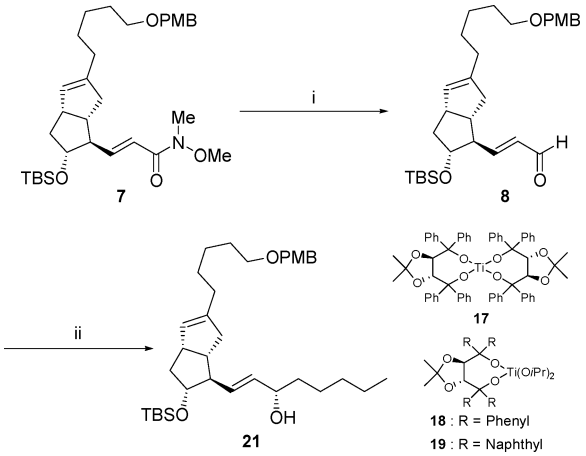
Entry	Substrate	Reduction method	d.r.[a]	Product	C15 configuration	Yield[b] (%)
1	**13**	(*R*)-Me–CBS	9 : 1	**15**	*S*	96
2	**13**	(*R*)-*n*-Bu–CBS	10 : 1	**15**	*S*	92
3	**14**	(*S*)-Me–CBS	6 : 1	**16**	*R*	95
4	**14**	(*S*)-*n*-Bu–CBS	7 : 1	**16**	*R*	86
5	**13**	(*S*)-BINAL-H	>35 : 1	**15**	*S*	91
6	**14**	(*R*)-BINAL-H	8 : 1	**16**	*R*	90

[a] Assigned from ^{1}H NMR analysis. [b] Isolated yields.



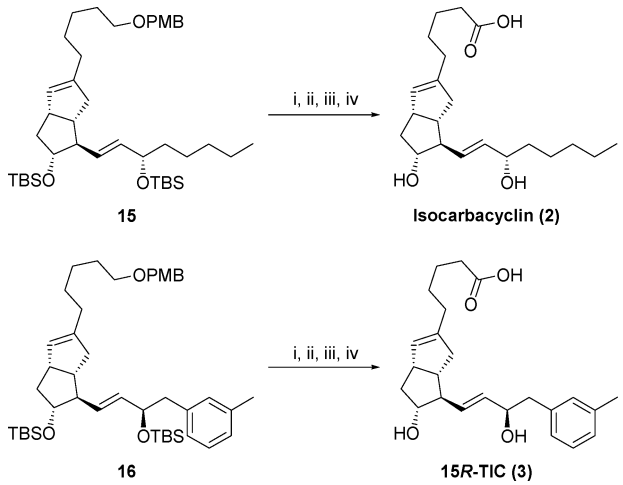
Scheme 4 Diastereoselective reduction of enone systems. *Reagents and conditions*: (i) Reduction (see Table 1); (ii) TBSCl, DMF, r.t. Yields for TBS protection of **15** and **16**, 96–100% and 96%, respectively.

(Scheme 5).[20] Changing the catalyst to **18** or **19** (documented to sometimes give better selectivities) did not have any effect in our case. The resulting allylic alcohol was protected with TBS to give previously described isocarbacyclin skeleton **15**. A similar strategy was planned for 15*R*-TIC using bis(3-methylbenzyl)zinc **22**.[19] Unfortunately, dibenzyl zinc **22** proved to be sluggish and unselective, compared to its alkyl analogue, due to its π-conjugation, resulting in 1,2-addition (where a d.r. of 5 : 1 was obtained, comparable to the reduction of enone **14**). The use of selected amino alcohols,[21] as a source of catalytic asymmetric induction, was also investigated, where diastereoselectivities obtained for both the isocarbacyclin and 15*R*-TIC substrates were inferior to those previously mentioned.[22]



Scheme 5 Diastereoselective Ti–TADDOL mediated addition. *Reagents and conditions*: (i) DIBAL-H, THF, −78 °C, 2 h, quant.; (ii) **17**/**18**/**19**, $Ti(OiPr)_4$, dipentyl zinc **20**, toluene, −50 °C, 82–84%.

The syntheses of the protected C1–C20 carbon skeletons of **15** and **16**, both represent the formal syntheses of isocarbacyclin (**2**) and 15*R*-TIC (**3**).[23] Treatment with DDQ, to give their corresponding primary alcohols, followed by Swern and Pinnick oxidations delivered the free carboxylic acids. Double TBS-ether deprotection was induced with a 0.5 N HCl solution to give isocarbacyclin (**2**) and 15*R*-TIC (**3**) (Scheme 6).



Scheme 6 Completion of isocarbacyclin and 15*R*-TIC syntheses. *Reagents and conditions*: (i) DDQ, CH_2Cl_2–H_2O (19 : 1); (ii) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2, −78 °C; (iii) $NaClO_2$, KH_2PO_4, 2,3-dimethyl-2-butene, *t*BuOH, H_2O; (iv) 0.5 N HCl, THF (over 4 steps for isocarbacyclin (**2**) and 15*R*-TIC (**3**), 79% and 74%, respectively.

Conclusions

We have synthesised, both isocarbacyclin (**2**) and 15*R*-TIC (**3**) *via* two ω-side chain addition strategies taking advantage of common synthetic intermediate **7**; firstly, a Grignard reagent addition strategy and secondly, after reduction to its corresponding aldehyde **8**, implementation of Seebach's highly diastereoselective alkylation chemistry. These routes should allow for considerable diversification of analogue synthesis; allowing the possibility to explore and understand the usefulness of these CNS ligands. Further research in our laboratories is currently ongoing, and subsequent results will be published in due course.

Acknowledgements

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18 Removal of the undesired diastereomers could be achieve by HPLC separation.

19 Dipentyl zinc reagents **20** and **22** were prepared from the parent Grignard compound by the procedure outlined in ref. 12.

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22 For isocarbacyclin: diastereoselectivities were lower than with Ti–TADDOL complexes, and for 15*R*-TIC: either no reaction was observed or only that with poor yield and/or diastereoselectivity.

23 Experimental data for both **15** and **16** match those reported in: N. A. Sheddan and J. Mulzer, *Org. Lett.*, 2006, **8**, 3101.

