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Access to Isocarbacyclin Derivatives via Substrate-Controlled Enolate Formation: Total Synthesis of 15-Deoxy-16-(*m*-tolyl)-17,18,19,20-tetranorisocarbacyclin

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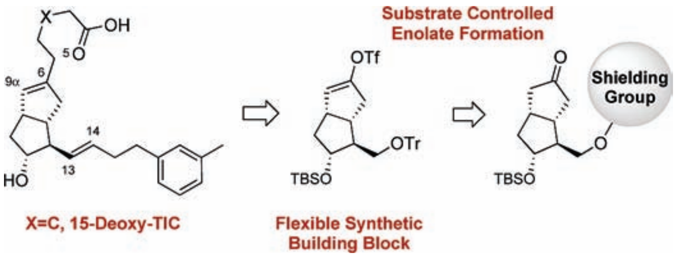
ABSTRACT



We describe a convergent and flexible synthesis of 15-deoxy-16-(*m*-tolyl)-17,18,19,20-tetranorisocarbacyclin (15-deoxy-TIC), a simple isocarbacyclin derivative. The synthesis takes advantage of two key step reactions: a regioselective deprotonation of the described ketone under substrate control which is then trapped, as the enol triflate, to generate the C6–C9α endocyclic double bond, followed by an sp^2–sp^3 Pd-catalyzed cross-coupling reaction (C5–C6) with a suitable primary alkyl Grignard reagent. Introduction of the C13–C14 (*E*)-double bond in the ω-side chain is performed by the Julia–Kocieński olefination.

In 1996, Takechi and co-workers reported the discovery of a novel subtype of the prostacyclin (PGI$_2$) receptor,[1] one having different properties compared with those of the known prostacyclin receptor. Isocarbacyclin (**4**), a stable analogue of prostacyclin,[2] which is a potent agonist for the known prostacyclin receptor, possesses high affinity for the novel subtype. Further investigation led to the design of the central nervous system (CNS)-specific PGI$_2$ ligands—15-deoxy-16-(*m*-tolyl)-17,18,19,20-tetranorisocarbacyclin (15-deoxy-TIC)[3] (**1**) and 15*R*-TIC[4] (**2**)—that exhibit neuronal survival-promoting activity. Ever since the discovery of these ligands, the biofunction of various TIC derivatives in the brain has been intensively investigated (Figure 1). These ligands have been successfully used to visualize the specific location of the IP$_2$ receptor for both in vitro and in vivo[5] systems by autoradiography of rat brain slices and positron emission tomog-

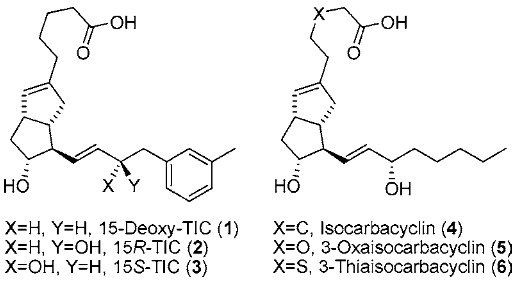


Figure 1. Isocarbacyclin and selected derivatives.

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[1] Takechi, H.; Matsumura, K.; Watanabe, Y.; Kato, K.; Noyori, R.; Suzuki, M.; Watanabe, Y. *J. Biol. Chem.* **1996**, *271*, 5901.

[2] Moncada, S.; Gryglewski, R.; Bunting, S.; Vane, J. R. *Nature* **1976**, *263*, 663.

[3] Suzuki, M.; Kato, K.; Watanabe, Y.; Satoh, T.; Matsumura, K.; Watanabe, Y.; Noyori, R. *Chem. Commun.* **1999**, 307.

[4] Suzuki, M.; Kato, K.; Noyori, R.; Watanabe, Y.; Takechi, H.; Matsumura, K.; Långström, B.; Watanabe, Y. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 334.

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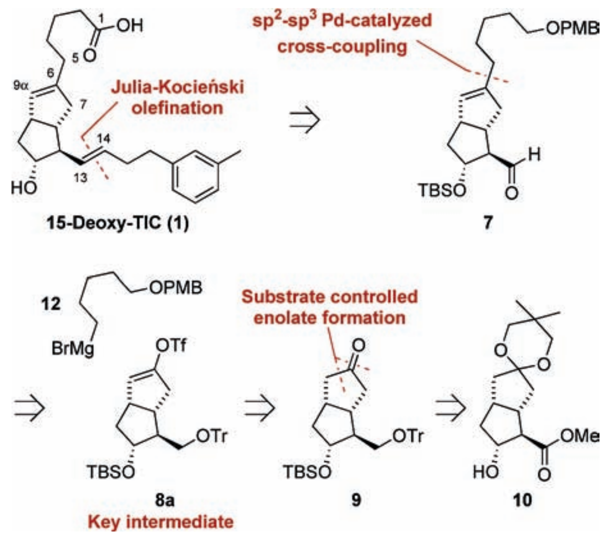
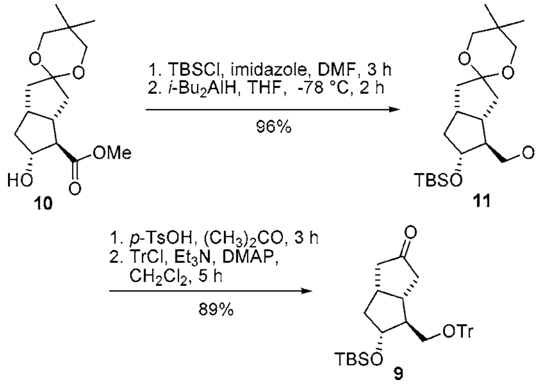
raphy (PET)[5,6]—a powerful noninvasive method for molecular imaging—of a living rhesus monkey,[7] using tritium- and ^{11}C-labeled TIC derivatives, respectively. 15-Deoxy-TIC (**1**) has shown binding to the CNS-type IP_2 receptor (IC_{50} = 3 nM) 10 times stronger than its 15*R*-TIC counterpart. Furthermore, the ratio of the potency of the binding affinity between 15-deoxy-TIC (**1**) and 15*R*-TIC (**2**) is actually correlated well with the biological activity. 15-Deoxy-TIC (**1**) has also shown an inhibitory effect on apoptosis of neuronal cells induced by high oxygen (50%) atmosphere at 10-fold lower concentration than 15*R*-TIC (**2**) (IC_{50} = 30 and 300 nM), respectively.[8]

Scheme 1



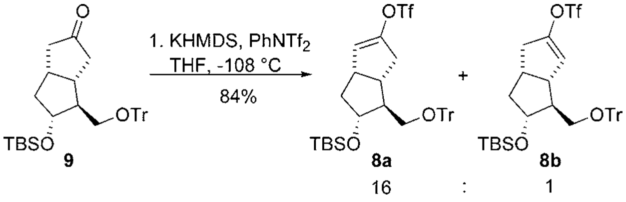
Our retrosynthesis of 15-deoxy-TIC (**1**) (Scheme 1) features the late-stage construction of the C13–C14 double bond in the *ω*-side chain by the Julia–Kocieñski olefination. The attachment of the α-side chain (C1–C5 skeleton) and construction of the C6–C9α[9] double bond has always proven to be a stumbling block and, as such, has received great attention over the years.[10–12] We decided that a disconnection at C5–C6 could exploit an sp^2–sp^3 palladium-catalyzed cross-coupling approach between vinyl triflate **8a**, and primary alkyl Grignard reagent **12**, to install the required α-side chain. This approach would also allow flexibility for the synthesis of other isocarbacyclin derivatives—3-oxaisocarbacyclin (**5**) and 3-thiaisocarbacyclin (**6**)—by appropriate choice of α-side-chain Grignard reagent. The second key step in our synthetic stategy is the generation of the five-ring endocyclic double bond. Previous work has been carried out on the desymmetrization of such bicyclic systems;[13] all, to the best of our knowledge, have employed the use of a chiral base. As we were first looking for a cost-efficient synthesis, available on gram scale, and one that avoided the use of an expensive chiral base, we envisaged that vinyl triflate **8a** could be synthesized via the regioselective deprotonation of the corresponding ketone under substrate control. To these ends we chose the sterically demanding trityl protecting group on the premise that due to the roof-shaped structure of ketone **9**, it would hinder the approach of the base at C7, leaving C9α open for deprotonation. Ketone **9** could then in turn be easily obtained in gram quantities from the known bicyclic methyl ester **10**,[14] with a mimimum of synthetic transformations.

Scheme 2



Starting from methyl ester **10**, after treatment with TBSCl and reduction with DIBAL-H, primary alcohol **11** was obtained (Scheme 2). Cleavage of the ketal protecting group and subsequent tritylation of the primary alcohol, ketone **9** was obtained in 89% yield over four steps.

Scheme 3



Ketone **9** in THF was treated with KHMDS (2 equiv) at −108 °C and kept at this temperature for a further 2 h followed by the addition of $PhNTf_2$ in THF, giving an inseparable mixture of compounds **8a** and **8b** (16:1 respectivly from ^{1}H NMR analysis) (Scheme 3). After recrystallization, needles of triflate **8a** were obtained which were then

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(5) Suzuki, M.; Noyori, R.; Långström, B.; Watanabe, Y. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 1053.

(6) Suzuki, M.; Doi, H.; Hosoya, T.; Långström, B.; Watanabe, Y. *Trends Anal. Chem.* **2004**, *23*, 595 and references therein.

(7) Watanabe, Y.; Suzuki, M.; Björkman, M.; Matsumura, K.; Watanabe, Y.; Kato, K.; Doi, H.; Onoe, H.; Sihver, S.; Andersson, Y.; Kobayashi, K.; Inoue, O.; Hazato, A.; Lu, L.; Bergström, M.; Noyori, R.; Långström, B. *Abstr. Pap. Neuroimage*, Aarhus, May 16–18, 1997; Vol. 5, A1.

(8) Satoh, T.; Ishikawa, Y.; Kataoka, Y.; Cui, Y.; Yanase, H.; Kato, K.; Watanabe, Y.; Nakadate, K.; Matsumura, K.; Hatanaka, H.; Kataoka, K.; Noyori, R.; Suzuki, M.; Watanabe, Y. *Eur. J. Neurosci.* **1999**, *11*, 3115.

(9) Prostacyclin numbering.

(10) Suzuki, M.; Koyano, H.; Noyori, R. *J. Org. Chem.* **1987**, *52*, 5583.

(11) Ogawa, Y.; Shibasaki, M. *Tetrahedron Lett.* **1984**, *25*, 1067.

(12) Ishikawa, T.; Ishii, H.; Shimizu, K.; Nakao, H.; Urano, J.; Kudo, T.; Saito, S. *J. Org. Chem.* **2004**, *69*, 8133.

subjected to X-ray diffraction, which combined with 2D NMR studies, unequivocally confirmed the regiochemistry to be that of the desired compound (Figure 2).

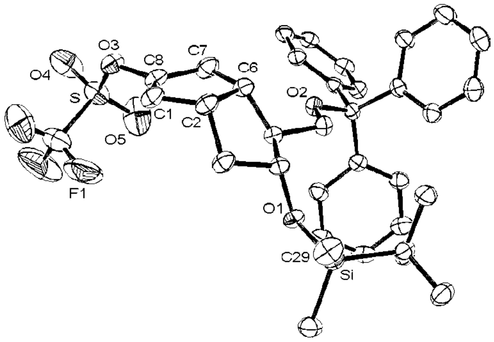
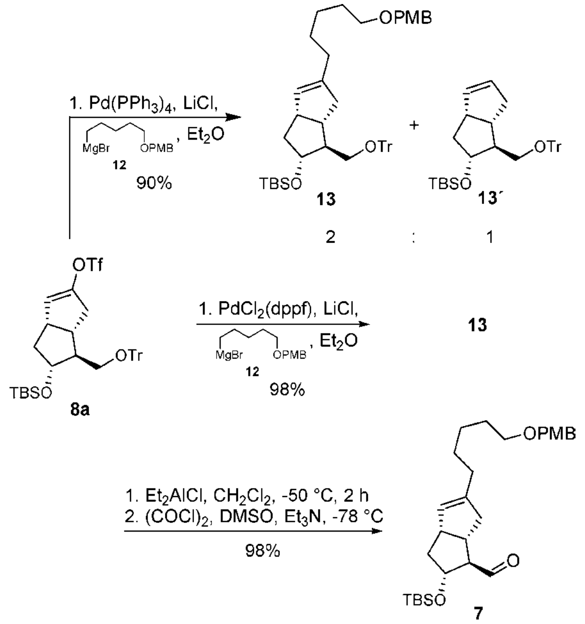


Figure 2. ORTEP-3[15] projection (ellipsoids: 50% probability) of triflate **8a**. Selected bond lengths: C1−C8, 1.32 Å; C7−C8, 1.49 Å.

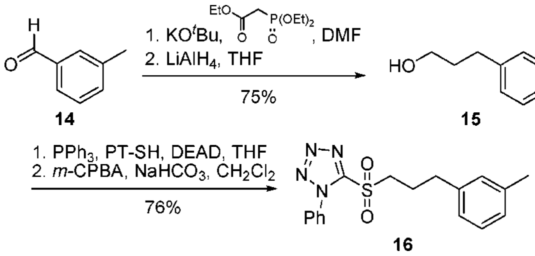
The coupling between enol triflate **8a** and alkyl Grignard reagent **12**,[16] under Pd-catalysis, in the presence of LiCl, was carried out following a modified Kuwajima protocol.[17] Upon treatment of enol triflate **8a**[18] with $Pd(PPh_3)_4$ (2 mol %) and subsequent addition of Grignard reagent **12** (1.1 equiv), a 2:1 mixture of **13** and *β*-hydride elimination product **13′** was obtained. In contrast, on treatment with $PdCl_2$(dppf) (2 mol %) as catalyst, cross-coupled product **13** was obtained as the only detectable product in 98% yield (Scheme 4). Chemoselective deprotection of the trityl group proved to be tricky under standard conditions,[19] resulting either in global deprotection or a 2:1 mixture of the desired primary alcohol and the diol resulting from additional TBS deprotection, respectively. After intensive investigation, we found that clean deprotection of trityl ether **13** was effected with Et_2AlCl at −50 °C. Swern oxidation of the resulting primary alcohol gave aldehyde **7** (98% yield over two steps).

Scheme 4



Synthesis of *ω*-side chain sulfone **16** was accomplished in four steps from commercially available *m*-tolyl aldehyde **14**. Horner−Wadsworth−Emmons olefination with triethyl phosphonoacetate yielded the corresponding α,*β*-unsaturated ethyl ester, which after complete reduction gave alcohol **15**. Mitsunobu reaction with 1-phenyl-5-mercaptotetrazole (PT-SH) followed by oxidation with *m*-CPBA furnished phenyl tetrazole **16** in 57% yield over four steps (Scheme 5).

Scheme 5



Despite the fact that this type of aldehyde has, in a previous synthesis of this compound,[3] been reported to be unstable under stongly basic conditions, we assumed that this referred to the Barbier conditions variation of the Julia−Kocieñski olefination. We therefore postulated that by using the premetalated species we should not encounter any difficulties. Treatment of sulfone **16** with KHMDS at −60 °C for 45 min, followed by the dropwise addition of aldehyde **7**, delivered *E*-olefin **17** (Scheme 6). NMR analysis showed no visible traces of the *Z*-isomer or epimerization at the C12 position. Deprotection of PMB ether **17** with DDQ yielded primary alcohol **18**, which was subsequently oxidized via Swern and Pinnick oxidations to carboxylic acid **19**. Finally, deprotection of the TBS ether was effected by TBAF to give 15-deoxy-TIC (**1**), albeit taking 4 days for the reaction to complete. Spectral comparison of our synthetic material with data provided by Professor Masaaki Suzuki matched perfectly.[20]

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(13) Vaulont, I.; Gais, H.-J.; Reuter, N.; Schmitz, E.; Ossenkamp, R. K. L. *Eur. J. Org. Chem.* **1998**, *805*, 5.

(14) (a) Weiss, U.; Edwards, J. M. *Tetrahedron Lett.* **1968**, *9*, 4885. (b) Petzoldt, K.; Dahl, H.; Skuballa, W.; Gottwald, M. *Liebigs. Ann. Chem.* **1990**, 1087.

(15) Farrugia, L. J. *J. Appl. Crystallogr.* **1997**, *30,* 565.

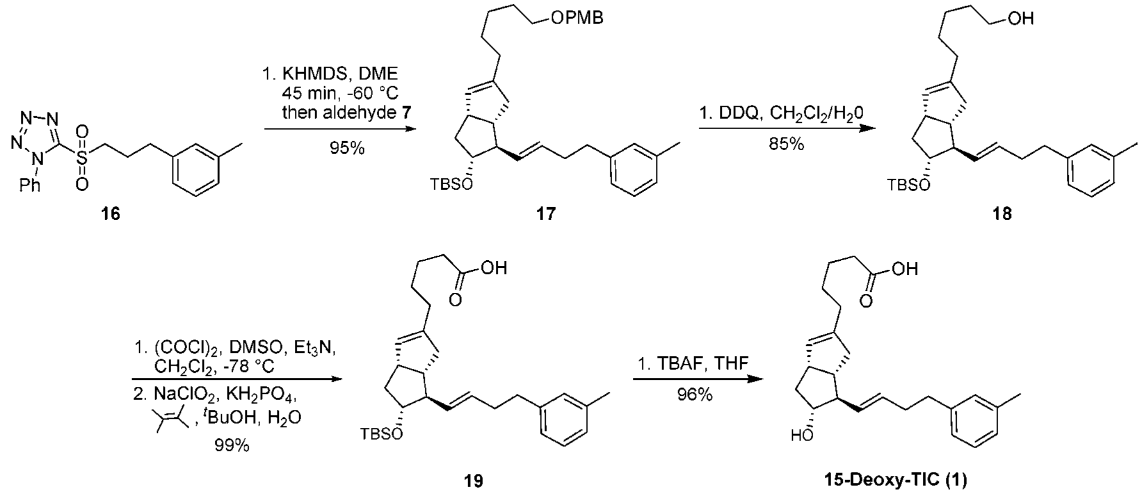
(16) Prepared from commerically available 1,5-pentandiol in three steps.

(17) (a) Enev, V.; Kählig, H.; Mulzer, J. *J. Am. Chem. Soc.* **2001**, *123,* 10764 and references cited within. (b) Morihira, K.; Hara, R.; Kawahara, S.; Nishimori, T.; Nakamura, N.; Kusama, H.; Kuwajima, I. *J. Am. Chem. Soc.* **1998**, *120,* 12980. (c) Hayashi, T.; Konishi, M.; Kobori, Y.; Kumada, M.; Higuchi, T.; Hirotsu, K. *J. Am. Chem. Soc.* **1984**, *106*, 158 and references cited within.

(18) A mixture of triflates **8a**/**b** (16:1) was used. After three steps and subsequent column chromatography to yield aldehyde **7**, the minor regioisomer could no longer be detected by ^{1}H NMR.

(19) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*; John Wiley & Sons: New York, 1999.

Scheme 6



In conclusion, the synthesis of 15-deoxy-TIC (**1**) was performed in 20 steps—13 steps along the longest linear sequence with a yield of 53%. A novel feature in our synthetic strategy is the generation of the troublesome C6–C9α double bond with great ease, via regiospecific ketone deprotonation under substrate control. Moreoverly, we have shown that a Pd-catalyzed cross-coupling can provide practical and easy access to α-side chain incorporation which could also be applied in the synthesis of other isocarbacylin analogues such as 3-oxaisocarbacyclin (**5**) and 3-thiaiso-carbacyclin (**6**).

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Supporting Information Available: Experimental procedures and selected NMR data for compounds **7**, **8a**, **9**, **12**, **13**, **15**–**19**, and **1** and X-ray crystallographic data for **8a** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) We thank Professor Masaaki Suzuki for the private communication of the 400 MHz ^{1}H and ^{13}C NMR data for 15-deoxy-TIC (**1**), allowing for a better comparison than with the originally published 270 MHz data; see ref 3.