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The Handy Use of Brown's P2-Ni Catalyst for a Skipped Diyne Deuteration: Application to the Synthesis of a $[D_4]$-Labeled F_{4t}-Neuroprostane

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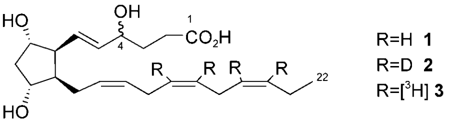
In memory of Marc Julia

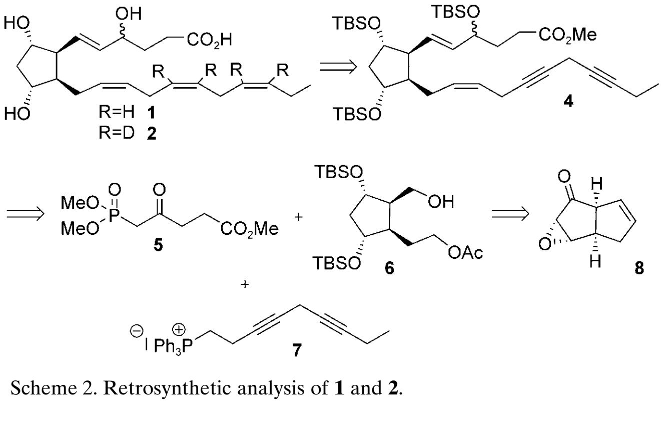
Since the discovery of isoprostanes (IsoPs), formed in vivo by free radical peroxidation of arachidonic acid (AA, C20:4 ω6), in 1990, these compounds have been extensively studied.[1] These metabolites have been shown to possess several biological activities. They are potent vasoconstrictors and produce vascular smooth muscle contraction as well as platelet aggregation.[2] Furthermore, they are currently used as an index of oxidative stress in numerous clinical trials. Indeed, the $[D_4]$-15-F_{2t}-IsoP (also called $[D_4]$-8-*epi*-$PGF_{2\alpha}$) is used as a standard to quantify IsoP levels in blood, plasma, and urine, as well as in various pathologies.[3] In 1998, new lipid oxidation metabolites derived from docosahexaenoic acid (DHA, C22:6 ω3), named neuroprostanes (NeuroPs) were discovered.[4] Since DHA is essentially located in the brain,[5] NeuroPs have been speculated to be potential markers of oxidative stress processes in various neurodegenerative disorders, including Alzheimer's disease (AD). Indeed, NeuroP levels are about two times higher in the temporal lobe tissue of AD patients than in healthy control subjects.[6] Consequently, the synthesis of deuterated NeuroP derivatives is required. To the best of our knowledge, the synthesis of such labeled compounds has rarely been studied. In fact, only one example of a deuterated NeuroP has been synthesized ($[D_4]$-7-F_{4t}-NeuroP).[7] Furthermore, Musiek et al.[6e] reported the used of $[^{18}O_2]$-17-F_{4c}-NeuroP as an internal standard, although recent studies showed its limited use in biological fluids (e.g., cerebrospinal fluid).[6h]

Taking into account that the fourth series of F_4-NeuroPs was reported as the most abundant series,[6e,8] an efficient and convergent access for the syntheses of the 4-F_{4t}-NeuroPs and labeled analogues was needed (Scheme 1). In 2000, our laboratory was the first to report the synthesis of 4-F_{4t}-NeuroP.[9] However, the strategy developed could not readily be used for the preparation of deuterated and tritiated derivatives. Herein, as an extension of this work and in connection with our ongoing program directed towards the total synthesis of IsoP and NeuroP derivatives, a new and flexible synthetic route to access both **1** and **2** is described.



Scheme 1. Structures of compounds 4(*R*,*S*)-F_{4t}-NeuroP (**1**), 16,17,19,20-$[D_4]$-4(*R*,*S*)-F_{4t}-NeuroP (**2**), and 16,17,19,20-$[^3H_4]$-4(*R*,*S*)-F_{4t}-NeuroP (**3**).

From a retrosynthetic point of view, it is anticipated that both **1** and **2** could be obtained from the regio- and stereoselective *cis* hydrogenation or deuteration reaction of the key skipped diyne **4** (Scheme 2), which could be easily pre-



Scheme 2. Retrosynthetic analysis of **1** and **2**.

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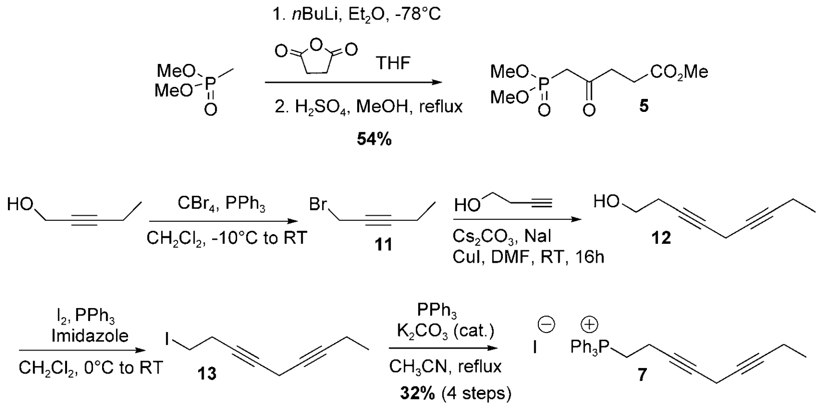
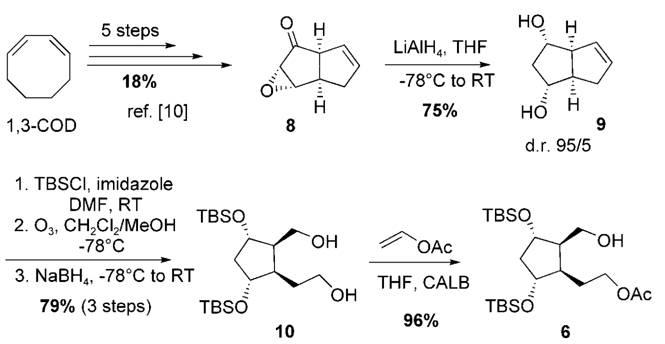


Scheme 4. Synthesis of the methyl 5-(dimethoxyphosphory)-4-oxopentanoate **5** and the nona-3,6-diynyltriphenylphosphonium iodide salt **7**.

pared from monoacetate **6** through successive olefination reactions using β-ketophosphonate **5** and phosphonium salt **7**. Monoacetate derivative **6** could arise from keto–epoxide intermediate **8**.[10]

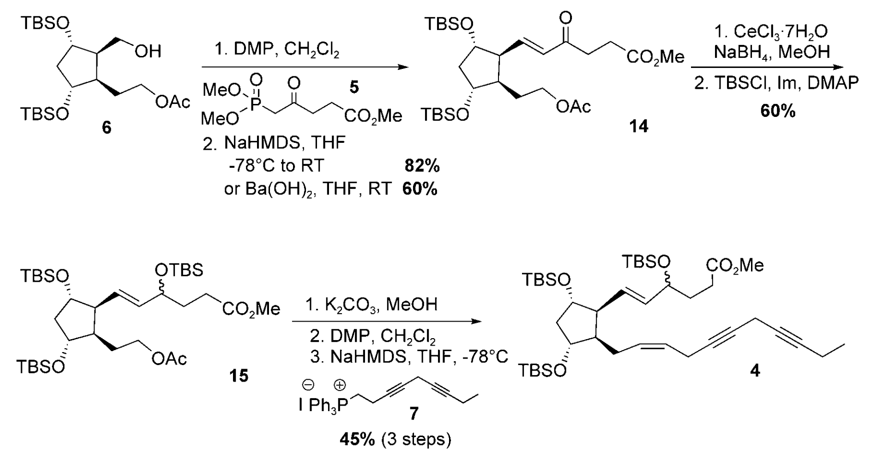


Scheme 3. Synthesis of monoacetate **6**.

The synthesis of the required monoacetate **6** began from the enantiomerically enriched bicyclic keto–epoxide **8** (>99% *ee*), which was readily prepared in five steps from 1,3-cyclooctadiene (1,3-COD) (Scheme 3).[10,11] Stereoselective reduction of the ketone functionality of compound **8** with $LiAlH_4$ at low temperature led to the formation of an epoxy alcohol intermediate that underwent regioselective epoxide ring opening upon warming the reaction mixture from −78 °C to RT. Under these conditions, the *cis*-1,3-diol **9** was isolated in 75% yield with an excellent diastereomeric ratio (d.r.) (95:5 *cis*/*trans*). After *tert*-butyldimethylsilyl (TBS) ether protection of the resulting *cis*-1,3-diol, ozonolysis, and reduction, the pseudo-symmetrical 1,5-diol **10** was acetylated by using the lipase B from *Candida antarctica* (CALB) and vinyl acetate, providing monoacetate **6** in excellent yield and selectivity.[12] It should be noted that this procedure is routinely run on a multigram scale.

Then we focused on the synthesis of the two lateral side-chain intermediates, that is, the nona-3,6-diynyltriphenylphosphonium iodide salt **7** and the methyl 5-(dimethoxyphosphoryl)-4-oxopentanoate **5** (Scheme 4). The β-ketophosphonate **5** was easily obtained in a one-pot, two-step procedure by the condensation reaction between succinic anhydride and dimethyl methylphosphonate lithium carbanion, followed by in situ esterification of the crude reaction mixture.[13] The synthesis of phosphonium salt **7** involves a four-step sequence. The bromination reaction of pent-2-yn-1-ol gave compound **11**, which was subjected to a copper-catalyzed cross-coupling reaction with but-3-yn-1-ol[14] under slightly modified conditions.[15] The resulting alcohol **12** was then converted to iodide **13** followed by a nucleophilic displacement with PPh_3 using Dawson and Vasser conditions[16] to give the phosphonium salt **7** in 32% overall yield.

Having established a reliable and scalable access to the three key intermediates **5**, **6**, and **7**, we performed a Dess–Martin oxidation[17] of alcohol **6**, followed by the Horner–Wadsworth–Emmons (HWE)[18] reaction with **5**, to introduce the "upper" side chain (Scheme 5). Although some epimerization occurs, diastereometrically pure enone **14** could be isolated in good yield after flash column chromatography (82%). It should be noted that no epimerization occurred when $Ba(OH)_2$ was used as a base, albeit enone **14** was obtained with a significant decreased yield (60%). Subsequent reduction of the enone **14** under Luche conditions[19] led to

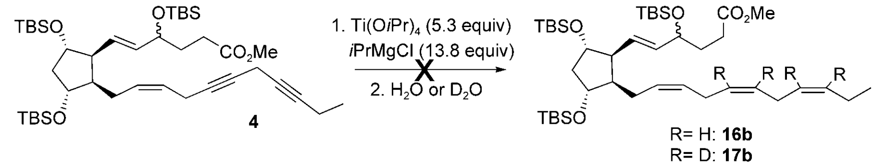


Scheme 5. Synthesis of the skipped diyne precursor **4**. DMAP = 4-dimethylaminopyridine, DMP = Dess–Martin periodinane, Im = imidazole.

an equimolar epimeric mixture of the allylic alcohol, which was then protected as a TBS ether (**15**). We next focused our efforts on the installation of the "lower" side chain. Thus, the skipped diyne **4** was readily obtained from compound **15** in 45 % overall yield through a three-step sequence involving deprotection of the acetate group, Dess–Martin oxidation, and then Wittig reaction[20] between the resulting aldehyde and the phosphonium salt **7**.[21]

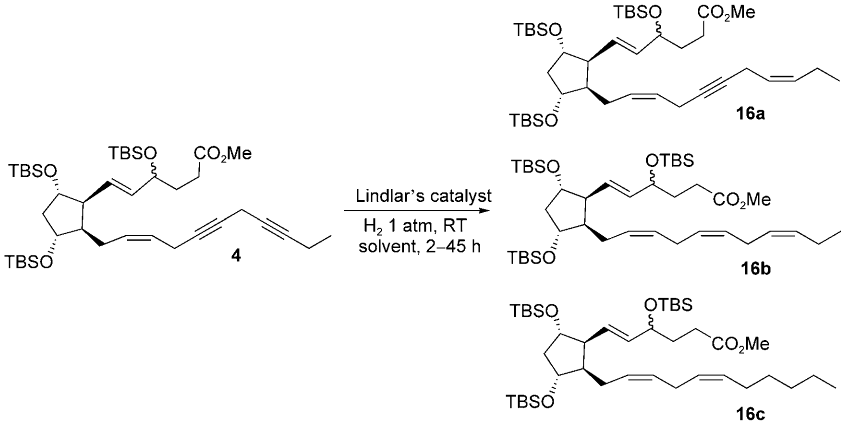
The next challenging issue was the regio- and stereoselective *cis* reduction of the alkyne functionalities of **4** to give the desired tetraene **16b** with *E*,*Z*,*Z*,*Z*-configured double bonds. Although several approaches for such a transformation have already been described in the literature,[22] this reaction proved to be more difficult than expected, and thus extensive optimization was necessary to find appropriate conditions. Based on a literature survey, Lindlar's palladium catalyst[23] (5 % Pd/$CaCO_3$ poisoned with lead) was revealed to be a good candidate for the stereoselective semihydrogenation of skipped diynes as indicated in many successful substrates.[24] The results of these experiments, summarized in Table 1, clearly showed that the regio- and stereochemical outcome of the reaction strongly depends on the solvent and catalyst loading. No conversion was observed when using 13 % of Lindlar's catalyst, irrespective of the solvents employed (Table 1, entries 1–3). Increasing the catalyst loading from 13 % to 33 and 77 % (and changing the solvent mixture) led to 52 and 40 % conversion, respectively, affording essentially the undesired, partially reduced product **16a**[25] (Table 1, entries 4 and 5). Encouraging results were obtained when the reaction was carried out in cyclohexane in the presence 134 % of catalyst, providing the required triene product **16b** in 80 % yield, although it was contaminated with 10 % of both starting material **4** and the partially reduced compound **16a** (Table 1, entry 6). Moreover, increasing the reaction time from 7 to 45 h gave full conversion, but led to the over-reduced product **16c** (Table 1, entry 7).

Since all attempts to isolate the required (*Z*,*Z*,*Z*)-triene **16b** were unsuccessful, the appealing titanium(II)-based methodology developed by Sato et al.[26] seemed promising, in regard to its successful use by Kitching and Hungerford[27] in the synthesis of deuterium-labeled linolenic acids. The main feature of this convenient one-pot procedure is that the alkoxytitanium–acetylene complex intermediate generated in situ from Ti(O*i*Pr)$_4$ (5.3 equiv) and *i*PrMgCl (13.8 equiv) in diethyl ether at −78 °C could provide direct access to both the reduced derivative **16b** and the deuterated compound **17b** by quenching with either H_2O or D_2O, respectively (Scheme 6). Unfortunately, in our case, treatment of compound **4** under the above reaction conditions resulted in the formation of an inseparable mixture of unidentified compounds.



Scheme 6. Titanium-based reduction of the skipped diyne **4**.

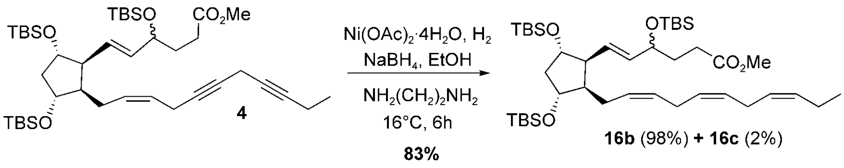
Table 1. Lindlar's catalyst reduction experiments with skipped diyne **4**.[a,25]



Entry	Lindlar's catalyst [wt %]	Solvents	*t* [h]	Ratio[b] **4/16a/16b/16c**
1	13	cyclohexane	2	100:0:0:0
2	13	EtOAc/EtOH (1:1)	2	100:0:0:0
3	13	THF/Et_3N (1:0.03)	2	100:0:0:0
4	33	EtOAc/EtOH/pyridine (13:6:1)	18	48:47:5:0
5	77	EtOAc/hexane/hexene (1:1:0.3)	3	60:40:0:0
6	134	cyclohexane	7	10:10:80:0
7	134	cyclohexane	45	0:10:45:45

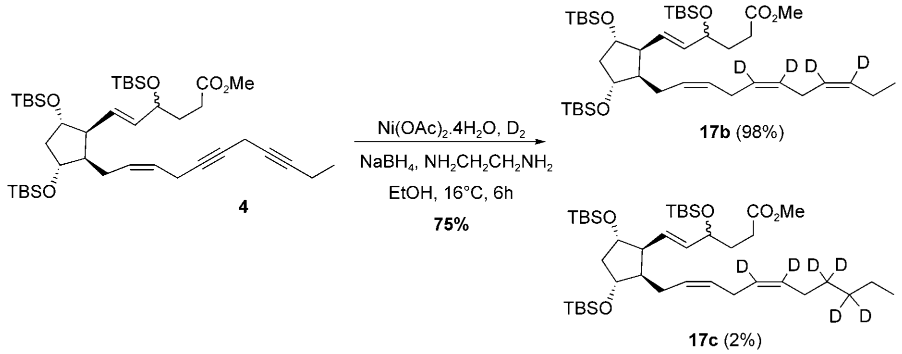
[a] Reaction conditions: hydrogen atmosphere, substrate **4** (30 mg), Lindlar's catalyst in solvent(s) (3 mL) at 20 °C. [b] Ratios were determined by GC/MS (EI) analysis.

A third approach was based on the use of the P2-Ni catalyst, pioneered by Brown and Ahuja in the 1970s.[28] This catalytic system is prepared by treating a vigorously stirred solution of nickel acetate tetrahydrate in 95 % ethanol with a solution of sodium borohydride in ethanol in a hydrogen atmosphere. This catalyst has previously been used for the synthesis of NeuroP derivatives.[29] In addition, this protocol has also been employed for the deuteration of skipped diyne intermediates for the synthesis of [D$_8$]-arachidonic acid,[30a] and an intermediate of leukotriene B$_4$.[30b] To our delight, a clean conversion of the skipped diyne **4** into the corresponding (*Z*,*Z*,*Z*)-triene **16b** was obtained in 83 % yield after flash column chromatography, when the reaction was performed at 16°C for 6 h. NMR spectroscopy analysis as well as GC/MS (EI) analysis revealed that the resulting sample was 98% pure with very small amounts (2%) of the inseparable unwanted over-reduced product **16c** (Scheme 7).



Scheme 7. P2-Ni-catalyzed regio- and stereoselective *cis* hydrogenation.

With this protocol in hand, and switching the hydrogen gas for deuterium gas, the (*Z*,*Z*,*Z*)-compound **17b** was isolated in 75% yield after purification by flash chromatography with 98% purity and only 2% of the unwanted compound **17c** (Scheme 8). Analysis by GC/MS of the reaction mixture showed a distribution in accordance with [D_4] incorporation and without traces of [D_3], [D_2], [D_1] or hydrogen incorporation. The 2% impurities of [D_4]-tetraene **17b** comprised only the over-reduced product **17c**.[31]



Scheme 8. P2-Ni-catalyzed regio- and stereoselective *cis* deuteration.[25]

Finally, tetra-*n*-butylammonium fluoride (TBAF)-mediated removal of the TBS groups followed by saponification of the methyl ester by using LiOH in THF/H_2O provided the 4(*R*,*S*)-F_{4t}-NeuroP **1** and its [D_4]-labeled analogue **2** in 86 and 78% overall yields, respectively (Scheme 9).

In conclusion, the total syntheses of the **1** and **2** via the pivotal intermediate **4** are reported. The key feature of our synthetic strategy involves a highly regio- and stereoselective *cis* hydrogenation or deuteration of the advanced skipped diyne intermediate **4** by Brown's P2-Ni catalyst. This strategy also permits us to envisage the synthesis of the tetratritiated analogue **3**. Finally, we hope that compound **2** will, in the near future, be used as a reliable internal standard for NeuroP quantification in biological fluids.[32]

Experimental Section

P2-Ni deuteration procedure: compound 17b: A solution of $NaBH_4$ in ethanol (1 M, 30 μL, 0.030 mmol, 0.77 equiv) was added to a suspension of $Ni(OAc)_2·4H_2O$ (3.0 mg, 0.012 mmol, 0.32 equiv) in ethanol (1.0 mL) in a D_2 atmosphere. After 30 min ethylenediamine in ethanol (1 M, 140 μL, 0.140 mmol, 3.70 equiv) was added to the black suspension. After 30 min the skipped diyne **4** (28 mg, 0.038 mmol, 1.0 equiv) in ethanol (0.6 mL) was also added. Before and after each addition, three cycles of vacuum/D_2 were realized. The reaction was then stirred for 6 h under D_2. The mixture was then filtered through a Celite pad, and rinsed with Et_2O. The solvents were removed under reduced pressure and the crude mixture was purified by flash chromatography (cyclohexane/Et_2O 95:5). The tetraene **17b** was obtained as a yellow oil (21 mg, 75%). $R_f = 0.86$ (cyclohexane/Et_2O 1:1); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 5.20$–5.50 (m, 4H), 4.05–4.20 (m, 3H), 3.70–4.00 (m, 2H), 3.75 (m, 1H), 3.65 (s, 3H), 3.10–3.65 (m, 3H), 3.50–3.70 (m, 1H), 2.15–2.45 (m, 3H), 1.95–2.10 (m, 4H), 1.70–2.00 (m, 3H), 1.40–1.60 (m, 2H), 0.97 (t, $^3J(H,H) = 7.5$ Hz, 3H), 0.70–0.90 (m, 27H), −0.15–0.10 ppm (m, 18H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 174.2$ (s, Cquat), 134.9 (s, CH), 134.8 (s, CH), 129.1 (s, CH), 128.8 (s, CH), 128.7 (s, CH), 128.5 (s, CH), 128.4 (s, CH), 128.3 (s, CH), 76.2 (s, CH), 76.0 (s, CH), 72.0 (s, CH), 52.4 (s, CH), 51.4 (s, CH_3), 50.0 (s, CH), 44.3 (s, CH_2), 33.2 (s, CH_2), 29.5 (s, CH_2), 26.3 (s, CH_2), 25.8 (s, CH_3 ×9), 25.6 (s , CH_2), 25.3 (s, CH_2), 20.4 (s, CH_2), 18.1 (s, Cquat ×3), 14.2 (s, CH_3), −4.4 (s, CH_3 ×2), −4.6 (s, CH_3 ×2), −4.7 (s, CH_3), −4.8 ppm (s, CH_3); IR: $\nu = 2954$, 2928, 2856, 1743, 1463, 1252, 1065 cm^{-1}; HRMS (ESI$^+$): *m*/*z*: calcd for $C_{41}H_{83}O_5Si_3$: 739.5548 [M+H]$^+$; found: 739.5549.

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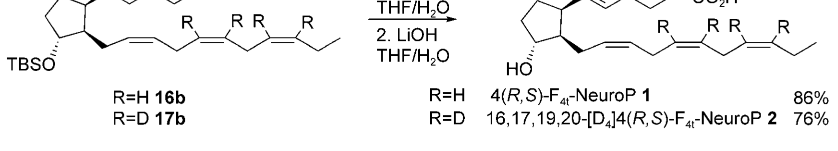

Scheme 9. Synthesis of **1** and its [D_4]-labeled analogue **2**.

Keywords: hydrogenation • isotopic labeling • neuroprostanes • nickel • skipped diynes

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[31] It is important to note that contrary to reference [30] we avoided the use of labeled reagents such as NaBD$_4$, [D$_4$]ethylenediamine, and [D$_6$]EtOH, because the hydrogen gas liberated during nickel(0) formation could be easily evacuated by vacuum/D$_2$ purges.

[32] While not yet commercially available, compound **2** is available to the research community.

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