Tetrahedron Letters 52 (2011) 3865–3867

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Flow chemistry approach for partial deuteration of alkynes: synthesis of deuterated taxol side chain

S. Chandrasekhar [a,*], B. V. D. Vijaykumar [a], B. Mahesh Chandra [a], Ch. Raji Reddy [a], P. Naresh [b]

[a] Organic Chemistry Division-I, Indian Institute of Chemical Technology, Hyderabad 500 007, India
[b] Center for Nuclear Magnetic Resonance, Indian Institute of Chemical Technology, Hyderabad 500 007, India

ARTICLE INFO

Article history:
Received 3 March 2011
Revised 10 May 2011
Accepted 11 May 2011
Available online 18 May 2011

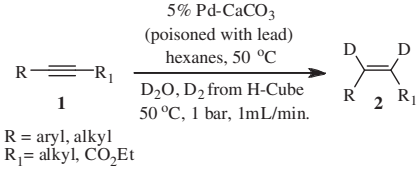
Keywords:
Flow chemistry
Partial deuteration
Sharpless asymmetric dihydroxylation
Deuterated taxol side chain

ABSTRACT

The partial deuteration of alkynes proceeds via a flow chemistry approach under Lindlar's heterogeneous catalysis to provide *cis*-dideuterated olefins in good yields. Further, dideuterated olefin has been successfully utilized for Sharpless asymmetric dihydroxylation followed by Mitsunobu reaction for the synthesis of deuterated taxol side chain.

Deuterium labeled compounds possess a wide range of applications in pharmaceuticals, environmental, materials and chemical sciences.[1] Although no product containing the deuterium atom has been found in nature, this atom constitutes important properties for the deuterated products. They are useful in studying metabolic pathways of bio-active molecules, detailed mechanism of chemical reactions etc.[2] In select cases of specifically modified molecules (by the incorporation of 'deuterium'), can positively impact certain drugs absorption, distribution, metabolism and excretion (ADME) properties, creating the potential for improved drug efficacy, safety, and tolerability. Thus, deuteration is exploited in various sites of the rapamycin, zilascorb, atazanavir etc., molecules to increase the potency of drug, reduce toxicity of the drug, reduce the clearance of the pharmacologically active moiety and improve the stability of the molecule.[3,4] Therefore the synthesis of deuterium labeled compounds has been receiving considerable attention by the research groups.

Usually deuterated compounds are synthesized by H–D exchange reaction under metal catalysis.[5] Besides, D_2-gas can be used to deuterate the organic molecule analogs by hydrogenation of olefins, acetylenes, cyanides etc. However, there is no report on partial deuteration of alkynes in a flow chemistry approach and further functionalization of resultant dideuterated olefins. This prompted us to explore the partial deuteration of acetylenes (**1**) using flow chemistry (H-cube) in the presence of Lindlar's catalyst (Scheme 1) involving a simple and inexpensive D_2-gas generation.[6]



Scheme 1. Partial deuteration of alkynes in H-cube.

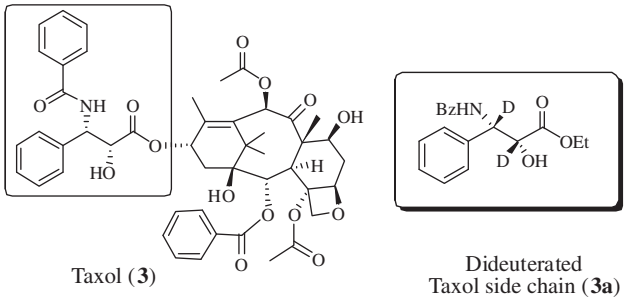


Figure 1. Structures of taxol and dideuterated taxol side chain.

Further, we successfully achieved the synthesis of deuterated taxol side chain **3a** by utilizing dideuterated (*Z*)-ethylcinnamate obtained via flow chemistry.

A noted example of the antitumor agent, taxol (**3**), contains *syn*-stereoisomer phenylisoserine side chain as its key pharmacophore

* Corresponding author. Tel.: +91 040 27193210; fax: +91 040 27160512.
E-mail address: srivaric@iict.res.in (S. Chandrasekhar).

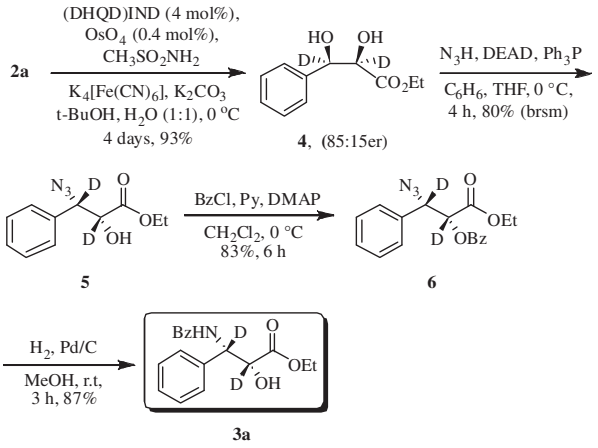
0040-4039/$ - see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2011.05.042

(Fig. 1). The approval of taxol (paclitaxel) as a therapeutic agent against ovarian and other types of cancer has continued to elicit interest in both the synthesis and biosynthesis of this molecule.[7]

As recently described by Fulop and co-workers,[8] the substrates were completely deuterated in the presence of 5% $Pd/BaSO_4$ catalyst. In our case, we have conducted the reaction using 5% Pd on $CaCO_3$ poisoned with lead (Lindlar's catalyst) to obtain the partially deuterated olefin. Ethyl 3-phenylpropiolate **1a** (100 mg) was dissolved in 100 mL HPLC-grade hexane. 5% $Pd/CaCO_3$ poisoned with lead (Lindlar's catalyst) was placed in the catalyst cartridge where the reaction takes place. The flow of the HPLC pump was adjusted to 1 mL/min, the temperature was set to 50 °C, and the pressure was set to minimum (1 bar). The collected eluent was evaporated to obtain the dideuterated olefin **2a** as a *Z*/*E* (7:1) mixture (Table 1, entry 1).[9]

Having able to partially reduce the acetylene into dideuterated (*Z*)-olefin, some other alkyne substrates were subjected to the above described protocol. Thus, alkyne **1b** was reduced to obtain exclusively *cis*-dideuterated olefin **2b** in 99% yield (Table 1, entry 2). Similar results were observed for **1c** as well as for propargylic alcohols **1d** and **1e** to furnish the corresponding dideuterated olefins **2c**, **2d**, and **2e** in good yields with *Z*-olefin as the major product (Table 1, entries 3, 4 and 5). The ratio of the products was determined by ^1H NMR. The *Z*-configuration of the major product was confirmed by the NOE studies on the reduced product of **2b** as well as on **2e**.[10]

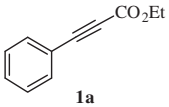
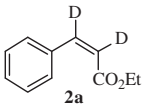
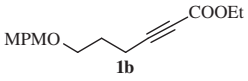
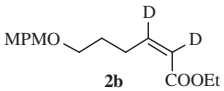
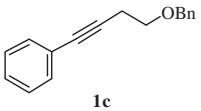
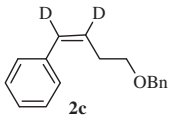
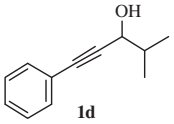
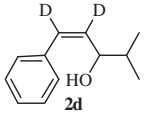
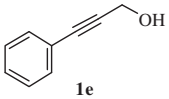
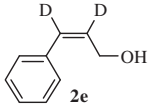
The (*Z*)-didueterated ethylcinnamate (**2a**) was further converted to α,β-dideuterated *N*-benzoyl 3-phenylisoserine **3a**, which is a deuterated analog of C-13 crucial side chain present in taxol (Scheme 2). Accordingly, deuterated olefin **2a** was treated under Sharpless asymmetric dihydroxylation (SAD) conditions using DHQD-IND ligand to furnish the erythro diol (2*R*,3*R*)-**4** in 92% yield.[11] To the best of our knowledge, this is the first example of SAD on a deuterated olefin which provided the diol **4** with 85:15 enantiomeric ratio (by chiral HPLC analysis).[12] At this stage we have decided to use this deuterated diol **4** for further transformations towards taxol side chain. Thus, diol **4** was treated with hydrazoic acid under Mitsunobu reaction conditions to afford azide **5** in 80% yield.[13] The azido alcohol **5** was treated with benzoylchloride to azidobenzoate **6** followed by the hydrogenation reaction, where the benzoyl group migrated from oxygen to the reduced amine providing the desired deuterated taxol side chain **3a**, in 72% yield (for two steps). All the deuterated compounds were fully characterized[14] by ^1H, ^2H and ^{13}C NMR, IR and mass spectra and the configurations assigned are tentative.



Scheme 2. Synthesis of dideuterated taxol side chain.

In summary, we have demonstrated the partial deuteration of alkynes using flow chemistry under Lindlar's catalysis. Importantly, further asymmetric functionalization involving dihydroxylation of deuterated olefin has also been demonstrated, which presents the indirect introduction of deuterium bearing asymmetric carbon. This was further converted to deuterated taxol side chain using Mitsunobu reaction as the key step.

Table 1
partial deuteration of alkynes by flow chemistry (H-cube)

Entry	Alkyne[a] (**1**)	Product[b] (**2**)	*Z*/*E*[c]	Yield[d] (%)
1	 **1a**	 **2a**	7:1	98
2	 **1b**	 **2b**	*Z* only	99
3	 **1c**	 **2c**	20:1	96
4	 **1d**	 **2d**	13:1	95
5	 **1e**	 **2e**	6:1	91

[a] All the compounds were prepared to 0.1% solutions in HPLC grade hexane.
[b] Structure showed for major product.
[c] All the *Z*/*E* ratios are characterized by NMR studies.
[d] Overall yield (*Z* and *E*) based on 2.

Acknowledgments

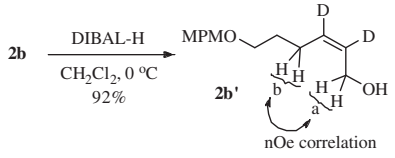
B.V.D.V., B.M.C., and P.N. are grateful to CSIR, New Delhi for research fellowship. The authors thank Dr. B. Jagadeesh, IICT for fruitful discussions and Heavy Water Board, Department of Atomic Energy for providing D_2O.

Supplementary data

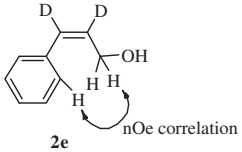
Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.05.042.

References and notes

1. Stovkis, E.; Rosing, H.; Beijnen, J. H. *Rapid Commun. Mass Spectrom.* **2005**, *19*, 401.
2. Baldwin, J. E.; Raghavan, A. S.; Hess, B. A.; Smentek, L. *J. Am. Chem. Soc.* **2006**, *128*, 14854.
3. Melvik, J. E.; Dornish, J. M.; Larsen, R. O.; Borretzen, B.; Oftebro, R.; Pettersen, E. O. *Anticancer Res.* **1992**, *12*, 33.
4. (a) Naicker, S.; Randall W. Yatscoff, R. W.; Foster, R. T., U.S. 6,710,053 B2, 2004.; (b) Laissue, J. A.; Burki, H.; Berchtold, W. *Cancer Res.* **1982**, *42*, 1125.
5. (a) Atzrodt, J.; Derdau, V.; Fey, T.; Zimmerman, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 7744; (b) Hanson, S. K.; Heinekey, D. M.; Goldberg, K. I. *Organometallics* **2008**, *27*, 1454; (c) Prechtl, M. H. G.; Holscher, M.; Ben-David, Y.; Theyssen, N.; Loschen, R.; Milstein, D.; Leitner, W. *Angew. Chem., Int. Ed.* **2007**, *46*, 2269; (d) Erdogan, G.; Grotjahn, D. B. *J. Am. Chem. Soc.* **2009**, *131*, 10354.
6. H-Cube® is a commercially available continuous flow reactor, which generates D_2 from D_2O in situ using an electrolytic process with a disposable catalyst cartridge system. This method avoids the use of expensive and dangerous D_2-gas cylinders.
7. Goodman, J.; Walsh, V. *The Story of Taxol: Nature and Politics in the Pursuit of an Anti-cancer Drug*; Cambridge University Press, 2000.
8. Mandity, I. M.; Martinek, T. A.; Darvas, F.; Fulop, F. *Tetrahedron Lett.* **2009**, *50*, 4372.
9. Hydrogenation of **1a** using H_2–Pd/C conditions gave the corresponding olefin **2a** in 97% yield with *E*/*Z* > 97:3 selectivity; see Refs.: (a) Shing, T. K. M.; Luk, T.; Lee, C. M. *Tetrahedron* **2006**, *62*, 6621; (b) Akbulut, N.; Hartsough, D.; Kim, J.-I.; Schuster, G. B. *J. Org. Chem.* **1989**, *54*, 2549.
10. (a) Substrate **2b** was subjected to DIBAL-H reduction to achieve allyl alcohol **2b′**, which was used for NOE studies and observed the NOE cross peaks between H_a and H_b as shown below.



(b) NOE-cross peaks observed in **2e**.



2e

11. (a) Wang, L.; Sharpless, K. B. *J. Am. Chem. Soc.* **1992**, *114*, 7568; (b) Xu, D.; Sharpless, K. B. *Tetrahedron Lett.* **1994**, *35*, 4685.
12. The enantiomeric ratio of the diol ester **4** was determined by chiral HPLC analysis (chiral pak AD-H: 250 × 4.6 mm column, mobile phase: 12% IPA/Hex, Flow rate: 1.0 mL/min, detection: 210 nm), er = 85:15. The ratio calculated is only for *Z*-isomer.
13. Soo, Y. K. *J. Org. Chem.* **2002**, *67*, 2689–2691.
14. *Spectral data for new compounds:* (**2a**): IR (neat): ν_{max} 2981, 2929, 1720, 1627, 1447, 1282, 1178, 1028, 766, 694, 667 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.62–7.55 (m, 2H), 7.39–7.29 (m, 3H), 4.17 (q, *J* = 7.5 Hz, 2H), 1.23 (t, *J* = 7.5 Hz, 3H); ^2H NMR ($CHCl_3$, 61.3 MHz): δ 6.94 (s, 1D), 5.95 (s, 1D); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 166.2, 143.0, 129.6, 128.9, 127.9, 60.3, 14.1; ESIMS (*m*/*z*): 178.
(**2b**): IR (neat): ν_{max} 2935, 2857, 1715, 1614, 1513, 1464, 1365, 1249, 1136, 1100, 1035, 820 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.19 (m, 2H), 6.80 (m, 2H), 4.39 (s, 2H), 4.12 (q, *J* = 7.1 Hz, 2H), 3.78 (s, 3H), 3.43 (t, *J* = 6.4 Hz, 2H), 2.71 (t, *J* = 7.5 Hz, 2H), 1.72 (m, 2H), 1.28 (t, *J* = 7.1 Hz, 3H); ^2H NMR ($CHCl_3$, 76.7 MHz): δ 6.28 (s, 1D), 5.80 (s, 1D); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 166.3, 159.0, 149.2, 130.2, 129.2, 119.5, 113.7, 72.5, 69.5, 59.7, 55.2, 29.1, 25.7, 14.2; ESIMS (*m*/*z*): 303 $[M + Na]^+$; HRMS(ESI): Calcd for $C_{16}H_{20}D_2NaO_4$ $[M+Na]^+$: 303.1379, found: 303.1373.
(**2b′**): IR (neat): ν_{max} 3397, 2924, 2857, 1615, 1514, 1458, 1247, 1037, 826 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.20 (d, *J* = 8.4 Hz, 2H), 6.82 (d, *J* = 8.4 Hz, 2H), 4.39 (s, 2H), 4.10 (s, 2H), 3.79 (s, 2H), 3.42 (t, *J* = 6.0 Hz, 2H), 2.18 (t, *J* = 6.9 Hz, 2H), 1.68 (br s, 1H), 1.65 (quin, *J* = 6.6 Hz, 2H); ^2H NMR ($CHCl_3$, 76.7 MHz): δ 5.68 (s, 1D), 5.52 (s, 1D). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 159.1, 130.4, 129.2, 113.7, 72.4, 68.7, 58.2, 55.2, 29.1, 23.7; ESIMS (*m*/*z*): 261 $[M+Na]^+$.
(**2c**): IR (neat): ν_{max} 3399, 2925, 1711, 1620, 1454, 1274, 894, 701 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.45–7.30 (m, 10H), 4.52 (s, 2H), 3.30 (t, *J* = 6.7 Hz, 2H), 2.33 (t, *J* = 6.7 Hz, 2H); ^2H NMR ($CHCl_3$, 61.3 MHz): δ 6.21 (s, 1D), 5.69 (s, 1D); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 133.6, 133.0, 131.5, 128.4, 127.9, 127.6, 72.9, 71.0, 28.1; ESIMS (*m*/*z*): 279 $[M+K]^+$.
(**2d**): IR (neat): ν_{max} 3374, 2925, 2960, 2872, 2853, 1716, 1489, 1466, 1027, 755 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.42–7.38 (m, 2H), 7.34–7.26 (m, 3H), 4.28 (d, *J* = 5.9 Hz, 1H), 1.96–1.76 (m, 1H), 1.80 (br s, 1H), 1.02 (d, *J* = 6.9 Hz, 3H), 1.00 (d, *J* = 6.9 Hz, 3H); ^2H NMR ($CHCl_3$, 61.3 MHz): δ 6.61 (s, 1D), 5.80 (s, 1D); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 131.6, 128.7, 128.2 (2 carbons), 72.1, 34.6, 18.1, 17.4; EI-MS (*m*/*z*): 179.
(**2e**): IR (neat): ν_{max} 3393, 3221, 2922, 2853, 1621, 1461, 1373, 884 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.40–7.10 (m, 5H), 4.44 (s, 2H), 2.05 (br s, 1H); ^2H NMR ($CHCl_3$, 76.7 MHz): δ 6.64 (s, 1D), 5.92 (s, 1D); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 136.6, 128.7, 128.3, 127.2, 62.0; EIMS (*m*/*z*): 135, 119.
(**4**): IR (neat): ν_{max} 3444, 2982, 2925, 1732, 1634, 1449, 1275, 1142, 1025, 765, 738, 701 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.38–7.24 (m, 5H), 4.11 (q, *J* = 7.1 Hz, 2H), 3.05 (br s, 2H), 1.15 (t, *J* = 7.1 Hz, 3H); ^2D NMR ($CHCl_3$, 61.3 MHz): δ 5.04 (s, 1D), 4.57 (s, 1D); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 171.9, 139.3, 128.2, 128.1, 126.4, 61.8, 13.9. ESIMS (*m*/*z*): 235 $[M+Na]^+$; HRMS(ESI): Calcd for $C_{11}H_{12}D_2NaO_4$ $[M+Na]^+$: 235.0910, found: 235.0916.
(**5**): IR (neat): ν_{max} 3456, 2924, 2105, 1733, 1637, 1449, 1264, 1151, 758, 700 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.54–7.32 (m, 5H), 4.29 (q, *J* = 7.1 Hz, 2H), 3.12 (br s, 1H), 1.62 (br s, 1H), 1.30 (t, *J* = 7.1 Hz, 3H); ^2D NMR ($CHCl_3$, 61.3 MHz): δ 5.53 (s, 1D), 4.97 (s, 1D); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 171.8, 135.4, 128.8, 128.7, 127.8, 62.4, 14.0; ESIMS (*m*/*z*): 260 $[M+Na]^+$; HRMS(ESI): Calcd for $C_{11}H_{11}D_2N_3NaO_3$ $[M+Na]^+$: 260.0975, found: 260.0975.
(**6**): IR (neat): ν_{max} 3449, 2978, 2925, 2104, 1726, 1638, 1450, 1278, 1110, 1069, 755, 708 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 8.12–8.06 (m, 2H), 7.63–7.56 (m, 1H), 7.51–7.31 (m, 7H), 4.13 (dq, *J* = 7.1, 1.5 Hz, 2H), 1.55 (br s, 1H), 1.14 (t, *J* = 7.1 Hz, 3H); ^2D NMR ($CHCl_3$, 61.3 MHz): δ 5.44 (s, 1D), 5.16 (s, 1D); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 167.3, 165.5, 134.4, 133.6, 130.0, 129.1, 128.8, 128.5, 127.5, 61.9, 13.8; ESIMS (*m*/*z*): 364 $[M+Na]^+$; HRMS(ESI): Calcd for $C_{18}H_{15}D_2N_3Na\ O_4$ $[M+Na]^+$: 364.1237, found: 364.1253.
(**3a**): IR (neat): ν_{max} 3422, 3353, 2977, 2929, 1717, 1624, 1523, 1489, 1276, 1139, 1122, 718, 701, 641, 607 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.80–7.74 (m, 2H), 7.56–7.24 (m, 8H), 7.04 (br s, 1H), 4.13 (m, 2H), 3.40 (br s, 1H), 1.30 (m, 3H); ^2D NMR ($CHCl_3$, 61.3 MHz): δ 5.75 (s, 1D), 4.60 (s, 1D); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 172.9, 166.8, 134.1, 131.7, 128.7, 128.6, 127.9, 127.0, 126.9, 62.7, 14.1; ESIMS (*m*/*z*): 338 $[M+Na]^+$; HRMS(ESI): Calcd for $C_{18}H_{17}D_2NNaO_4$ $[M+Na]^+$: 338.1332, found: 378.1353.