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# Synthesis of iodinated analogues of all *trans* retinoic acid (ATRA) for SPECT imaging

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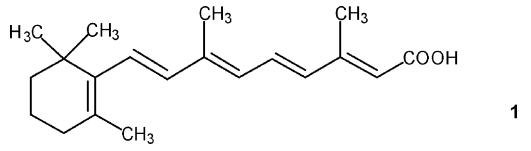
**Abstract**—Two derivatives of all *trans* retinoic acid in which one of the methyl groups has been replaced by iodine have been prepared.

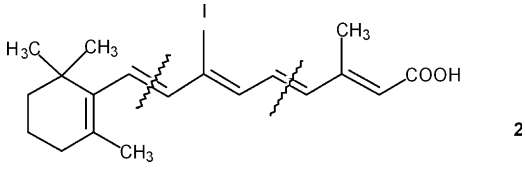

A common situation met in the procurement of tracers for SPECT (Single Photon Emission Computed Tomography) medical imaging is that the introduction of a label onto a drug leads to a compound, which differs in its overall architecture from the parent molecule. However there are some cases in which it is conceivable to introduce the marker into a region of the molecule in a way, which is expected to have minimal adverse effects on its physicochemical properties, compared to those of the original molecule. $^{123}I$ is a γ-emitting radionucleide commonly used for SPECT and since iodine resembles a methyl group in terms of bulkiness and lipophilicity, the preparation of a derivative in which iodine would replace a methyl group present in the drug could be a fruitful approach in the design of SPECT-compatible tracers.



1

Retinoids are inducers of cell differentiation and apoptosis[1] and, more specifically, ATRA (all *trans* retinoic acid) (**1**) is used to induce remission of acute promyelocytic leukaemia (APL) in current oncological practice.[2,3] Since there is a need for imaging of ATRA uptake, the synthesis of derivatives suitable for SPECT has been considered; in light of the above considerations, replacement by iodine of one of the ATRA methyl groups has been favoured[4] and the preparation of two such derivatives is presented.

The preparation (see Scheme 1) of the first of these, 9-iodo-9-nor-ATRA(**2**), was planned by assembly of C10+C4+C5 fragments:



2

The C4 iodinated partner **3**[5] was obtained after desymmetrization[6] of but-2-yne-1,4-diol; this was followed by formation of an alanate,[7] which was reacted with molecular iodine[8] to get **3**; since the stereochemical outcome of this process is controlled by the adjacent hydroxymethyl group, the *Z* configuration was assigned.[9] Oxidation of **3** was performed efficiently with IBX[10] and the intermediate aldehyde[11] was condensed with phosphonate **4** under the conditions found suitable for such Wadsworth–Emmons–Horner condensations.[12] This afforded **5**, the configuration of which was assigned

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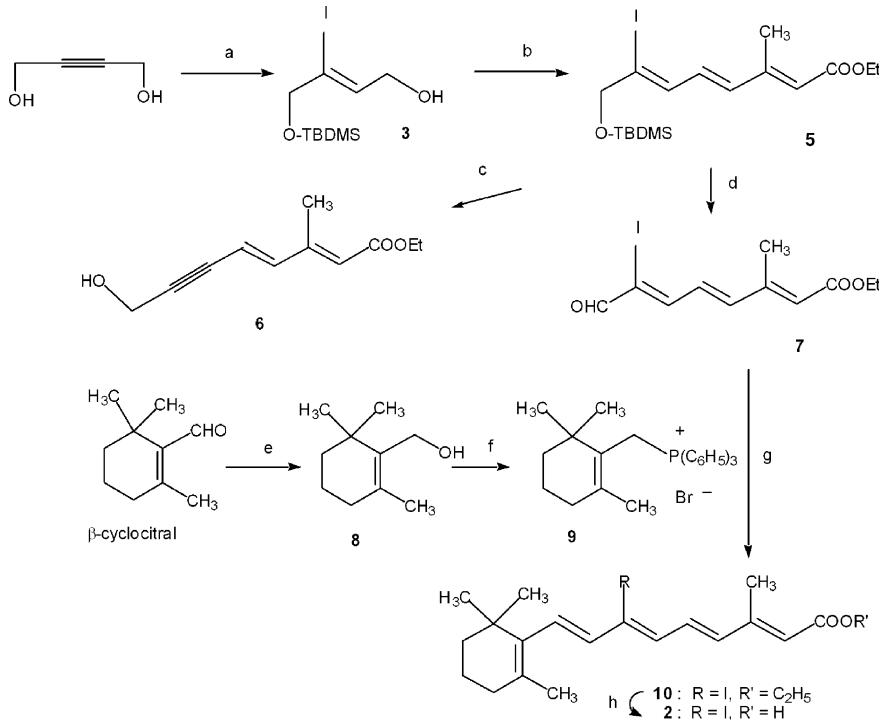
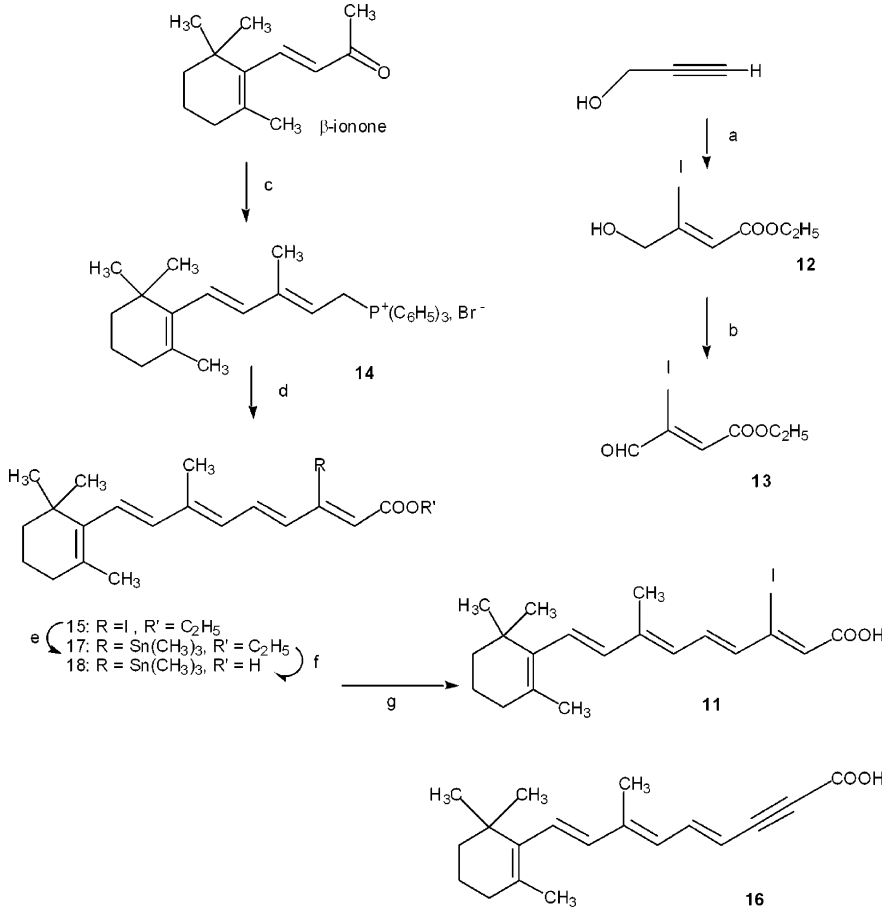



**Scheme 1.** Reagents and conditions: (a) (1) TBDMSiCl, $Et_3N$, DMAP—Ref. 6, (2) Red-Al, then $I_2$ (91%). (b) (1) IBX (95%); *E*-$(EtO)_2P(O)CH_2$–$C(CH_3)$=CHCOOEt (**4**), LDA, DMPU (94%). (c) TBAF. (d) (1) HF-py (95%); (2) Swern (92%). (e) $NaBH_4$–$CeCl_3 \cdot 7H_2O$, $CH_3OH$, 4 °C (97%). (f) Ref 15. (g) **9**, −70 °C, *n*-BuLi, then **7** (93%). (h) 1.75 M NaOH, 1:1 $H_2O$/EtOH), 50 °C, 45 min (98%).




**Scheme 2.** Reagents and conditions: (a) (1) *n*-BuLi, TMSiCl; (2) *n*-BuLi, ClCOOEt; (3) LiI, AcOH (76%). (b) Swern (88%). (c) (1) $CH_2$=CHMgBr; (2) $PPh_3 \cdot HBr$—Ref 18. (d) (1) LDA, DMPU, then **14** (74%). (e) $Pd(PPh_3)_4$, $Me_6Sn_2$, DIEA (55%). (f) NaOH (1.75 M in 1:1 $H_2O$/EtOH), 50 °C, 45 min. (g) $I_2/CH_2Cl_2$ (63% from **17**).

as *E* from the large coupling constant observed for the newly introduced vinylic protons.[13] At this stage, removal of the silyl ether using tetrabutylammonium fluoride led to loss of iodine (to give alkyne **6)** but the use of milder conditions (HF-py) allowed regeneration of the hydroxyl group; this was followed by Swern oxidation to get **7**.[14] The β-cyclogeranyl partner **9** was conventionally obtained[15] from β-cyclogeraniol **8**, which, in this work, was obtained by $NaBH_4$/$CeCl_3{\cdot}7H_2O$ reduction of β-cyclocitral thus improving literature procedures.[16] Condensation of the ylide derived from **9** with freshly prepared **7** afforded ester **10**, the saponification of which led to 9-iodo-9-nor-retinoic acid, **2**.[17]

To get the 13-iodo-13-nor-ATRA isomer (**11**) the assembly of a C15 fragment[18] with **13**[19] was planned (Scheme 2). The iodinated derivative **12** was prepared in three sequential steps from propargylic alcohol by (1) in situ transient protection of the hydroxyl group,[20] (2) formation of the acetylide followed by its quenching with ethyl chloroformate and (3) 1–4 addition of lithium iodide to the conjugated ester. The *Z* stereochemistry of the product **12** can be deduced from mechanistic considerations[21] but it has been proven by observation of an NOE effect between the vinylic proton and the methylene group.[22] Oxidation of **12** by manganese dioxide[19] gave a mixture of *E*/*Z* aldehydes as was the case when IBX was used; however Swern oxidation gave pure **13**. This sensitive aldehyde was condensed with the ylide derived from **14**,[18] which gave ester **15**.[23] In contrast with results for the vinylogous 9-iodo series (i.e., saponification of **10**), cleavage of the ester group of **15** proved troublesome: whether acidic or basic conditions were used, the only product, which could be characterized was acetylenic derivative **16**.[24] This situation could be overcome by conversion of **15** to tin derivative **17**[25] whose saponification to **18** could be achieved satisfactorily. Iodolysis of the tin–carbon bond then gave 13-iodo-13-nor-ATRA, **11**.[17] In view of the lability of the carbon–iodine bond in this compound however (particularly under basic conditions), 9-iodo-9-nor-ATRA **2** would appear to be a more suitable candidate for SPECT imaging.[26]

## References and notes


1. Simoni, D.; Rondanin, R.; Baruchello, R.; Roberti, M.; Rossi, M.; Grimaudo, S.; D'Alessandro, N.; Invidiata, F. P.; Tolomeo, M. *Pure Appl. Chem.* **2001**, *73*, 1437.
2. Degos, L.; Wang, Z. Y. *Oncogene* **2001**, *20*, 7140.
3. Cassinat, B.; Chevert, S.; Zassadowski, F.; Balitrand, N.; Guillemot, I.; Menot, L.; Degos, L.; Fenaux, P.; Chomienne, C. *Blood* **2001**, *98*, 2862.
4. For a derivative of 9-*cis* retinoic acid in which iodine substitutes a vinylic hydrogen see: Klaus, M.; Lovey, A. J.; Mohr, P.; Rosenberg, M. Eur. Patent Appl. No. 728742, 1996.
5. This compound has recently been obtained by a free-radical approach; see: Commeiras, L.; Santelli, M.; Parrain, J.-L. *Tetrahedron Lett.* **2003**, *44*, 2311.
6. MacMahon, S.; Fong, R.; Baran, P. S.; Safonov, I.; Wilson, S. R.; Schuster, D. I. *J. Org. Chem.* **2001**, *66*, 5449.
7. Red-Al has been shown to be the reagent of choice for this transformation: Denmark, S. E.; Jones, T. K. *J. Org. Chem.* **1982**, *47*, 4595; for related examples see: Blanchette, M. A.; Malamas, M. S.; Nantz, M. H.; Roberts, J. C.; Somfai, P.; Whritenour, D. C.; Masamune, S. *J. Org. Chem.* **1989**, *54*, 2817; Denis, R. C.; Gravel, D. *Tetrahedron Lett.* **1994**, *35*, 4531.
8. Corey, E. J.; Katzenellenbogen, J. A.; Posner, G. H. *J. Am. Chem. Soc.* **1967**, *89*, 4245.
9. The *Z* configuration of **3** has been secured by its conversion to nakienone B. See: Pour, M.; Negishi, E.-I. *Tetrahedron Lett.* **1996**, *37*, 4679.
10. More, J. D.; Finney, N. S. *Org. Lett.* **2002**, *4*, 3001.
11. This aldehyde ($^1$H NMR, 200 MHz, $CDCl_3$, $\delta$: −0.10 (s, 6H, $SiCH_3$), 0.92 (s, 9H, $SiC(CH_3)_3$), 4.42 (d, $J = 2.1$ Hz, 2H, H-4), 6.69 (dt, $J = 6.5$ Hz, $J = 2.1$ Hz, 1H, H-2), 9.67 (d, $J = 6.5$ Hz, 1H, H-1). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$: −5.7 ($SiCH_3$), 18.2 ($SiC(CH_3)_3$), 26.7 ($C(CH_3)_3$), 72.3 (C-4), 128.8 (C-3), 129.1(C-2), 196.5 (C-1) can be purified by column chromatography but should be freshly prepared before use.
12. Mata, E. G.; Thomas, E. J. *J. Chem. Soc., Perkin Trans. 1* **1995**, 785.
13. **5**: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$: −0.10 (s, 6H, $SiCH_3$), 0.93 (s, 9H, $SiC(CH_3)_3$), 1.28 (t, $J = 7.1$ Hz, 3H, $OCH_2CH_3$), 2.34 (d, $J = 1.1$ Hz, 2H, $CH_3$-3), 4.12 (q, $J = 7.1$ Hz, 2H, $OCH_2CH_3$), 4.35 (s, 2H, H-8), 5.83 (s, 1H, H-2), 6.41 (d, $J = 14.7$ Hz, 1H, H-4), 6.66 (m, 2H, H-5, H-6). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$: −5.3 (Si–$CH_3$), 13.7 ($CH_3$), 14.3 ($CH_3$), 18.3 ($SiC(CH_3)_3$), 25.8 ($C(CH_3)_3$), 59.8 ($OCH_2CH_3$), 71.7 (C-8), 111.7 (C-7), 120.6 (C-2), 131.1, 135.1, 138.8 (C-4, C-5, C-6), 151.7 (C-3), 166.8 (C-1).
14. In contrast to oxidation of **3**, the use of IBX resulted here in configurational scrambling as a 1:1.8 *E*/*Z* mixture was detected.
15. Dawson, M. I.; Hobbs, P. D.; Chan, R. L.-S.; Chao, W.-R. *J. Med. Chem.* **1981**, *24*, 1214.
16. Pommer, H. *Angew. Chem.* **1960**, *72*, 811; Büchi, G.; White, G. D. *J. Am. Chem. Soc.* **1964**, *86*, 2884; Behr, D.; Wahlberg, I.; Nishida, T.; Enzell, C. R. *Acta Chem. Scand.* **1977**, *31B*, 793; Crombie, B. S.; Smith, C.; Varnavas, C. Z.; Wallace, T. W. *J. Chem. Soc., Perkin Trans. 1* **2001**, 206.
17. NMR assignments of ATRA, for $^1$H see: Perly, B.; Pappalardo, G. C.; Klaus, M.; Montoneri, E. *Z. Naturforsch.* **1988**, *43b*, 1072; for $^{13}$C see: Bernard, M.; Ford, W. T.; Nelson, E. C. *J. Org. Chem.* **1983**, *48*, 3164;
**2**: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$: 1.10 (s, 6H, $CH_3$-1), 1.4–1.7 (m, 4H, H-2, H-3), 1.73 (s, 3H, $CH_3$-5), 2.04 (m, 2H, H-4), 2.39 (large s, 3H, $CH_3$-13), 5.85 (s, H-14), 5.83 and 6.64 (AB system, $J = 15$ Hz, H-7, H-8), 6.46 (d, $J = 11$ Hz, $H_{10}$), 6.48 (d, $J = 15$ Hz, $H_{12}$), 7.03 (dd, $J = 11$ Hz, $J = 15$ Hz, 1H, $H_{11}$). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$: 14.0 ($CH_3$-13), 19.1 (C-3), 21.8 (C-5), 28.9 ($CH_3$-5), 33.3 (C-4), 34.4 (C-1), 39.6 (C-2), 112.4 (C-9), 119.2 (C-14), 132.1, 136.9 (C-5, C-6), 134.2, 135.2, 137.7, 138.3, 139.1 (C-7, C-8, C-10, C-11, C-12), 154.5 (C-13), 171.2 (C-15). **11**: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$: 1.04 (s, 6H, $CH_3$-1), 1.47 (m, 2H, H-2), 1.61 (m, 2H, H-3), 1.72 (s, 3H, $CH_3$-5), 2.04 (m+s, 5H, H-4, $CH_3$-5), 6.20, 6.37 (AB system, $J = 15.7$ Hz, H-7, H-8), 6.39 (m, 1H), 6.62 (large s, 1H) and 7.13–7.26 (m, 2H): (H-10, H-11, H-12, H-14). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 13.1 ($CH_3$-9), 19.2 (C-3), 21.8 ($CH_3$-5), 29.0 ($CH_3$-1), 33.2 (C-4), 34.3 (C-1), 39.7 (C-2), 124.7 (C-13), 127.0, 128.6, 128.7, 130.5, 145.2 (C-7, C-10, C-11, C-12, C-14), 130.9 (C-5), 137.0 (C-8), 137.6 (C-6), 143.6 (C-9), 168.0 (C-15).
18. Curley, R. W., Jr.; DeLuca, H. F. *J. Org. Chem.* **1984**, *49*, 1941.

19. Shinada, T.; Yoshihara, K. *Chem. Pharm. Bull.* **1996**, *44*, 264.
20. O-TMS propargyl alcohol is *very* moisture sensitive and was directly used after in situ formation that is without isolation. For use of a *tert*-butyldimethylsilyl ether, see: Piers, E.; Chong, M.; Morton, H. E. *Tetrahedron* **1989**, *45*, 363.
21. Ma, S.; Lu, X. *J. Chem. Soc., Chem. Commun.* **1990**, 1643.
22. Shinada, T.; Sekiya, N.; Boojkova, N.; Yoshihara, K. *Tetrahedron* **1999**, *55*, 3675.
23. Under those conditions, NMR analysis of the crude material showed 92% *E* configurational purity; note that a 6 to 4:1 *E*/*Z* ratio was observed after reaction with the ylide derived from **9** (see Ref. 19).
24. For the elimination of iodine in such a conjugated ester, see: Brisdon, B. J.; Brown, D. W.; Willis, C. R.; Drew, M. G. B. *J. Chem. Soc., Dalton Trans.* **1986**, 2405.
25. The less toxic bis(tributyl)ditin was ineffective for this transformation.
26. To enable the preparation of material with high specific activity, **2** was converted to the corresponding trimethyltin derivative $(Me_3Sn)_2$/Pd (0), 73%); **2** could be regenerated (90%) after reaction with iodine.