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Stereoselective Synthesis of 9-*cis*-Retinoic Acid By Suzuki Reaction

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Abstract: The entire polyenic side chain of ethyl 9-*cis*-retinoate (**7**) has been stereoselectively synthesized and attached to the hydrophobic ring by a high-yielding thallium-accelerated Suzuki cross-coupling reaction. The Suzuki reaction partners, tetraenyl iodide **18** and alkenyl organoborane **19**, are more conveniently used immediately after generation from their precursors. Alternative approaches using either the Stille reaction or a Suzuki reaction with a shorter polyenic component proved less efficient. The highly convergent sequence can be adapted to the preparation of analogs of 9-*cis*-retinoic acid (**2**), the natural ligand for the retinoid X (RXR) subfamily of nuclear receptors.

The nuclear receptors for retinoids[1] are currently key molecular targets for cancer chemoprevention, due to the presence of retinoid response elements in a large number of genes involved in cell proliferation and differentiation.[2] Whereas retinoic acid receptors (RARs) have a high affinity for both *trans*-retinoic acid (**1**, Scheme 1) and its isomer 9-*cis*-retinoic acid (**2**), the latter is the natural ligand of the retinoid X receptors (RXRs).[1] The six isoforms of these proteins (RARα, RARβ, RARγ; and RXRα, RXRβ, RXRγ) are transcription factors that activate transcription by interaction with their target genes through specific DNA-binding domains.[1b] In particular, RXR is a central regulator of hormone action through heterodimerization with other proteins of the nuclear receptor superfamily,[1a] including the RARs, the thyroid hormone receptor (TR), the peroxisome proliferator-activated receptors (PPARs) and the vitamin D receptor (VDR).[1b] In order to target tissue-specific genes, the design and synthesis of retinoids selective for RXRα, RXRβ or RXRγ isoforms showing reduced toxicity is required.[3] The instability of the polyene chain becomes of particular concern when designing novel retinoids and most structural modifications have incorporated some of the double bonds into rings to avoid undesirable olefin reactivity.[3] However, metabolic studies with isotopically labelled ligands[4] demand the stereoselective synthesis of retinoids with the polyene side chain intact. Two highly stereoselective approaches to 9-*cis*-retinoic acid (**2**) have recently been published.[4,5] Bennani[4a] generated the 9-*cis* geometry by addition of a methylcuprate to a propargylic nitrile and the olefin chain was completed by a Horner-Wadsworth-Emmons reaction.[4a] We have reported a new approach to 9-*cis*-retinoids based on the isomerization of 10-arylsulfenate-11,12-dehydroretinoids, which may involve a complex cascade that is likely to be pericyclic in nature.[5] We wish to report herein a novel stereoselective approach to 9-*cis*-retinoic acid (**2**) based on the Suzuki reaction[6] starting from 2,2,6-trimethylcyclohexanone (**11**) and enynol **8** (Scheme 2).

As an extension of our reported procedure for the stereocontrolled preparation of ethyl retinoate (**6**) and its ring-demethylated analogs by Stille reaction between tetraenylstannane **4** and cycloalkenyltriflates such as **3** (Scheme 1),[7] we first considered the coupling of triflate **3** and isomeric tetraenylstannane **5** (synthesis shown in

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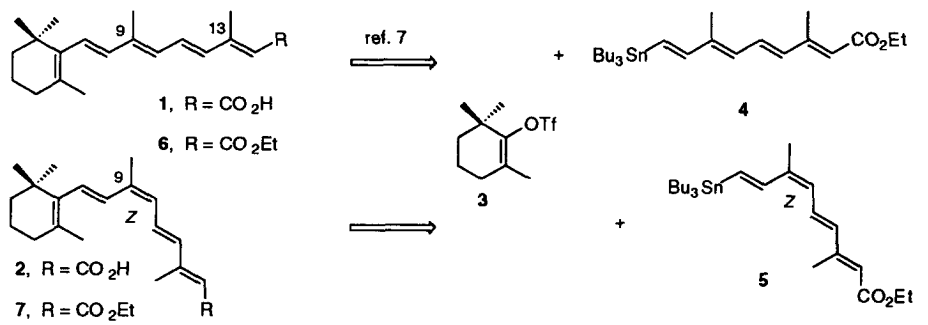
Scheme 3) as the most straightforward approach to ethyl 9-*cis*-retinoate (**7**) and thence to target **2**. However, even at the lowest temperature that effected the coupling of **5** and the sterically hindered triflate **3** (Pd_2dba_3, $AsPh_3$, NMP, 40 °C),[8] the reaction took place with isomerization of the *Z* double bond, affording mixtures of products **7** and **6**.

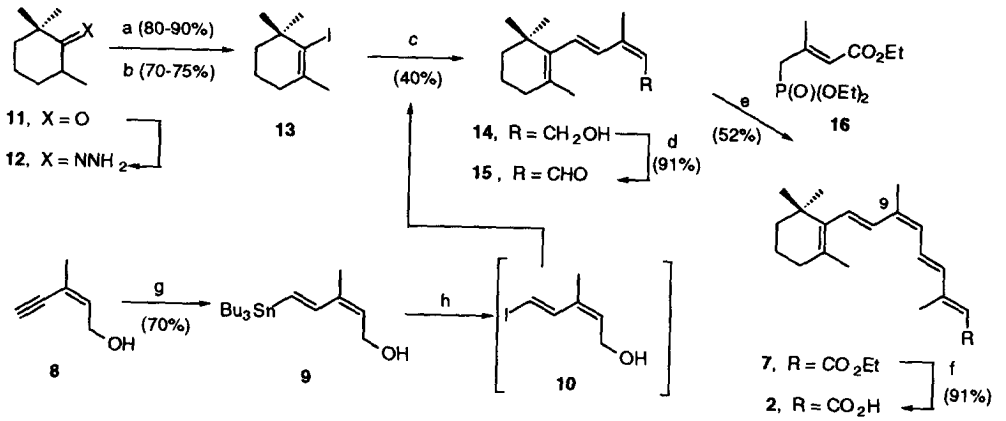
Scheme 1



Whilst searching for a more reactive electrophile, we prepared alkenyl iodide **13** (Scheme 2) starting from the hydrazone of 2,2,6-trimethylcyclohexanone (**12**) following a reported modification[9b] of Barton's procedure.[9a] Although coupling of **5** and **13** could be induced at ambient temperature (25 °C), conversions were unacceptably slow (*ca.* 25% conversion after 24 h). Coupling of the less sensitive dienyl stannane **9** (Scheme 2) to either triflate **3** or iodide **13** also proceeded sluggishly at room temperature.

Since it has been demonstrated that the Suzuki coupling is more tolerant to steric hindrance than the Stille coupling,[10] we turned our attention to the latter, which has been successfully used in our group for the formation of the C10-C11 single bond of the retinoid side chain.[11] In our experience, the main limitation of this approach to retinoids[11a-c] and other sensitive polyenes[11e-f] is the handling and purification of the boronic acid (or ester) intermediates. To overcome these difficulties, Keay *et al.* reported the cross-coupling reaction of aryl and vinyl halides with *in situ*-generated organoboranes,[12a] obtained by treatment of the organolithium precursor with trimethylborate. Since vinyl lithium derivatives can be prepared by Shapiro reaction starting from the corresponding hydrazones, both reactions (Shapiro-Suzuki) have been combined to couple C_{sp2} fragments without the need to isolate the corresponding intermediates.[12b] Despite extensive experimentation, we did not succeed in generating an organolithium reagent from hindered hydrazone **12** or other analogs (trisylhydrazone, tosylhydrazone) using the Shapiro reaction. As an alternative, treatment of iodide **13** with *t*-BuLi in THF at -78 °C for 30 min, followed by addition of trimethylborate and stirring at room temperature led to the presumed boronic ester intermediate.[12a] Sequential addition of iodide **10** (prepared by tin/iodine exchange[13a] of known[13b,c] stannyldienol **9**), $Pd(PPh_3)_4$ and 10% aq. TlOH[14] provided, after stirring for 6 h at 25 °C, trienol **14** in a disappointing yield of 40%. Oxidation of **14** with TPAP/NMO[15] afforded trienal **15**. Without purification (2*Z*-dienals rearrange to 2H-pyrans)[16] aldehyde **15** was treated with the carbanion derived from diethyl 3-(ethoxycarbonyl)-3-methylprop-2-en-yl phosphonate (**16**) in the presence of DMPU[4a] first at -115 °C and then at -40 °C, to give ethyl 9-*cis*-retinoate (**7**) in 52% overall yield. Lastly, basic hydrolysis of **7** yielded the desired 9-*cis*-retinoic acid (**2**).[17]

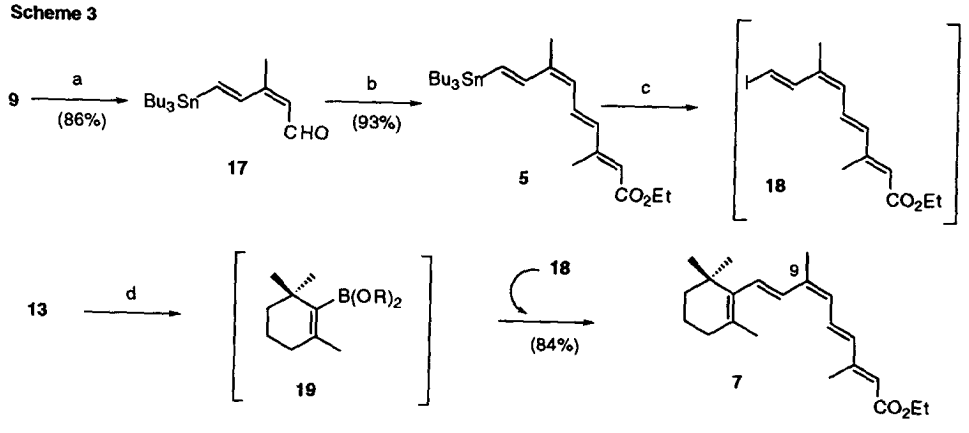
Scheme 2



(a) $H_2NNH_2.H_2O$, Et_3N, EtOH. (b) I_2, DBN, ether; (c) 1. *t*-BuLi, THF, -78 °C. 2. $B(OMe)_3$, -78 °C. 3. $Pd(PPh_3)_4$, **10**, 10% aq. TlOH, 25 °C, 12 h; (d) TPAP, NMO, 0 to 25 °C, 4 h; (e) *n*-BuLi, THF, DMPU, **16**, -115 to -40 °C; (f) 5N KOH, EtOH, 70 °C; (g) *n*-BuLi, *n*-Bu_3SnH, CuCN, THF, -78 to -40 °C; (h) I_2, CH_2Cl_2, 25 °C.

Low yields in the above sequence could be traced back to the instability of the dienyl iodide **10**, as well as to the lability of (2*Z*,4*E*)-trienol **14**, which suggested the need for a more convergent strategy avoiding the handling of these unstable intermediates. However, independent generation of iodide **18** from tetraenylstannane **5** (Scheme 3) revealed its highly unstable nature, and it underwent extensive decomposition upon attempted isolation.We finally found it more convenient to couple the *in situ*-generated tetraenyliodide **18** and the *in situ*-generated organoborane. Accordingly, after obtaining **18** by titration of tetraenylstannane **5** with a solution of iodine in CH_2Cl_2, the solvent was evaporated, THF was added, and this solution was immediately added dropwise to a THF solution of $Pd(PPh_3)_4$ and the organoborane **19** freshly prepared from **13**. After stirring for 10 min at room temperature, 10% aq. TlOH[14] was added, and stirring was continued for 6 h. Work up and purification provided ethyl 9-*cis*-retinoate (**7**) in 84% yield from starting components **13** and **5**.

Scheme 3



(a) MnO_2, K_2CO_3, CH_2Cl_2, 0 to 25 °C, 2 h; (b) *n*-BuLi, THF, DMPU, **16**, -115 to -40 °C; (c) I_2, CH_2Cl_2, 25 °C; (d) 1. *t*-BuLi, THF, -78 °C. 2. $B(OMe)_3$, -78 to 0 °C. 3. $Pd(PPh_3)_4$, **18**, 10% aq. TlOH, 25 °C, 6 h.

In summary, we have developed a new synthetic approach to 9-*cis*-retinoic acid (**2**), the natural ligand of the RXR family of nuclear receptors, by Suzuki coupling which avoids the isolation of organoboranes and other unstable intermediates. The convergent sequence proceeds under mild reaction conditions and can be extended to the preparation of analogs of ligand **2** with modifications on the hydrophobic ring by selecting the series of demethylated triflates,[7] invaluable congeners for the structure-activity studies currently ongoing in our group.

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References

1. For recent reviews, see: (a) Evans, R. M. *Science* **1988**, *240*, 889-895. (b) Mangelsdorf, D. A.; Evans, R. M. *Cell* **1995**, *83*, 841-850. (c) Rosen, J.; Day, A.; Jones, T. K.; Jones, E. T. T.; Nadzan, A. M.; Stein, R. B. *J. Med. Chem.* **1995**, *38*, 4855-4874.
2. Hong, W. K.; Sporn, M. B. *Science* **1997**, *278*, 1073-1077.
3. (a) Vuligonda, V.; Lin, Y.; Chandraratna, R. A. S. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 213-218. (b) Beard, R. L.; Colon, D. F.; Song, T. K.; Davies, P. J. A.; Kochhar, D. M.; Chandraratna, R. A. S. *J. Med. Chem.* **1996**, *39*, 3556-3563. (c) Canan Koch, S. S.; Dardashti, L. J.; Hebert, J. J.; White, S. K.; Croston, G. E.; Flatten, K. S.; Heyman, R. A.; Nadzan, A. M. *J. Med. Chem.* **1996**, *39*, 3229-3234.
4. (a) Bennani, Y. L. *J. Org. Chem.* **1996**, *61*, 3542-3544. (b) Bennani, Y. L.; Boehm, M. F. *J. Org. Chem.* **1995**, *60*, 1195-1200. Ito *et al.* have reported the generation of 9-*cis*-retinoic acid (**2**) from the iron tricarbonyl complex of the same trienal **15**.[4a] See: Wada, A.; Hiraishi, S.; Takamura, N.; Date, T.; Aoe, K.; Ito, M. *J. Org. Chem.* **1997**, *62*, 4343-4348.
5. de Lera, A. R.; Castro, A.; Torrado, A.; López, S. *Tetrahedron Lett.* **1998**, *39*, 4575-4578.
6. For recent reviews on the Suzuki reaction, see: (a) Martin, A.; Yang, Y. *Acta Chem. Scand.* **1993**, *47*, 221-230. (b) Suzuki, A. *Pure Appl. Chem.* **1994**, *66*, 213-222. (c) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457-2483.
7. Domínguez, B.; Iglesias, B.; de Lera, A. R. *J. Org. Chem.* **1998**, *63*, 4135-4139.
8. Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, *113*, 9585-9595.
9. (a) Barton, D. H. R.; Bashiardes, G.; Fourrey, J-L. *Tetrahedron* **1988**, *44*, 147-162. (b) Di Grandi, M. J.; Jung, D. K.; Krol, W. J.; Danishefsky, S. J. *J. Org. Chem.* **1993**, *58*, 4989-4992.
10. Anderson, J. C.; Namli, H.; Roberts, C. A. *Tetrahedron* **1997**, *53*, 15123-15134.
11. (a) Torrado, A.; López, S., Alvarez, R.; de Lera, A. R. *Synthesis* **1995**, 285-293. (b) Torrado, A.; Iglesias, B.; López, S.; de Lera, A. R. *Tetrahedron* **1995**, *51*, 2435-2454. (c) de Lera, A. R.; Iglesias, B.; Rodríguez, J.; Alvarez, R.; López, S.; Villanueva, X.; Padrós, E. *J. Am. Chem. Soc.* **1995**, *117*, 8220-8231. (d) Alvarez, R.; López, S.; de Lera, A. R. *Nat. Prod. Lett.* **1995**, *6*, 127-132. (e) Alvarez, R.; Herrero, M.; López, S.; de Lera, A. R. *Tetrahedron* **1998**, *54*, 6793-6810. (f) Alvarez, R.; de Lera, A. R. *Tetrahedron: Asymmetry* **1998**, *9*, 3065-3072.
12. (a) Maddaford, S. P.; Keay, B. A. *J. Org. Chem.* **1994**, *59*, 6501-6503. (b) Passafaro, M. S.; Keay, B. A. *Tetrahedron Lett.* **1996**, *37*, 429-432.
13. (a) Friesen, R. W.; Loo, R. W. *J. Org. Chem.* **1991**, *56*, 4821-4823. (b) Fokokawa, F.; Hamada, Y.; Shioiri, T. *Tetrahedron Lett.* **1993**, *34*, 6559-6562. (c) Betzer, J.-F.; Delagoge, F.; Muller, B.; Pancrazi, A.; Prunet, J. *J. Org. Chem.* **1997**, *62*, 7768-7780.
14. Uenishi, J.; Beau, J.-M.; Armstrong, R. W.; Kishi, Y. *J. Am. Chem. Soc.* **1987**, *109*, 4756-4758.
15. Griffith, W. P.; Ley, S. V.; Whitcombe, G. P.; White, A. D. *J. Chem. Soc., Chem. Commun.* **1987**, 1625-1627.
16. (a) Kluge, A. F.; Lillya, C. P. *J. Am. Chem. Soc.* **1971**, *93*, 4458-4463. (b) Chandraratna, R. A. S.; Okamura, W. H. *Tetrahedron Lett.* **1984**, *25*, 1003-1006.
17. Spectroscopic data for **2** matched those previously published (refs. 4 and 5). Particularly revealing, for identification purposes, is the chemical shift of H_8 in the 9-*cis*-isomer, which appears downfield (6.65 ppm) relative to that of *trans*-retinoic acid **1** (6.18 ppm).