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Tetrahedron Letters 44 (2003) 3093–3096

TETRAHEDRON LETTERS

Trienylboronic acid, a versatile coupling tool for retinoid synthesis; stereospecific synthesis of 13-aryl substituted (11*Z*)-retinal

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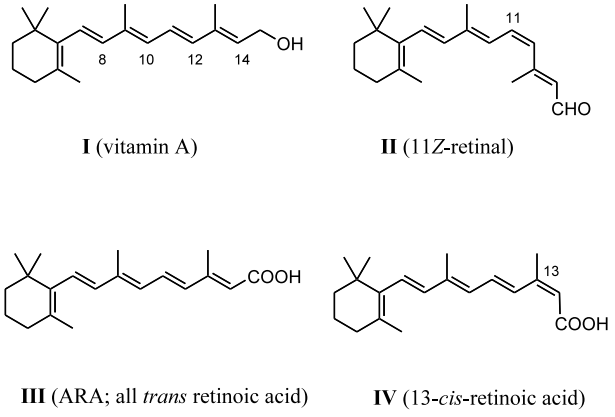
Received 27 January 2003; revised 17 February 2003; accepted 21 February 2003

Abstract—Trienylboronic acid **1a** was prepared from iodotriene **3**, which was coupled with (2*Z*,4*Z*)-3-aryl-5-iodo-2,4-pentadienol **9** by Suzuki coupling reaction to give geometrically pure 13-aryl substituted (11*Z*)-retinol **10**. Oxidation of **10** gave 13-aryl substituted (11*Z*)-retinal **11**.

1. Introduction

Retinoids play important roles in biological actions in organisms.[1] These stereo-structures, shown in Figure 1, generally consist of a consecutively conjugated pentaene. They are generally unstable and sensitive to light, acid, base and heat to raise isomerization or polymerization. The stereochemistry of olefinic bonds is highly important in relation to the biological activities.[2] Various synthetic methods for the synthesis of such conjugated polyenes, including Wittig or Wittig–Horner–Emmons reaction and Julia olefination reaction have been reported.[3] These methods can be used for the synthesis of geometrically stable polyenes but were not suitable for the synthesis of polyenes possessing less stable (*Z*)-olefinic bond or large substituent groups on the olefinic carbons.[4] A transition metal-catalyzed cross-coupling reaction is effective in such cases and has been used for the geometry control in conjugated polyene syntheses.[5] In fact, some retinoids and their analogues have been prepared by metal catalyzed cross-coupling reactions.[6] Considering the flexible synthetic approach for retinoids I–IV (Fig. 1), connection between a C_{10} and C_{11} sigma-bond by a cross-coupling reaction using trienylmetal species **1** and iododiene is a favorable and straightforward approach, as shown in Scheme 1. However, since a few approaches have been successfully utilized,[7] a versatile and reliable C_1–C_{10} trienylmetal reagent is desired as a cross-coupling unit for general and flexible retinoid synthesis. In this paper, we describe the preparation of trienylboronic acid **1a** as an isolable trienylmetal reagent and the cross-coupling reaction for the first synthesis of a 13-aryl substituted (11*Z*)-retinal.[8]



I (vitamin A) **II** (11*Z*-retinal)

III (ARA; all *trans* retinoic acid) **IV** (13-*cis*-retinoic acid)

Figure 1.

2. Preparation of 1a and cross-coupling reaction

Initially, we attempted to prepare trienylstannane **1b** from the known dienyne **2**[9] by stannylmagnesiation, although it was found to be unstable and rather difficult to handle.[10] We therefore used trienylboronic acid **1a** instead of **1b** as a C_1–C_{10} unit (Scheme 2).

Keywords: trienylboronic acid; Suzuki coupling; conjugated pentaene; 11*Z*-retinal; iododiene.

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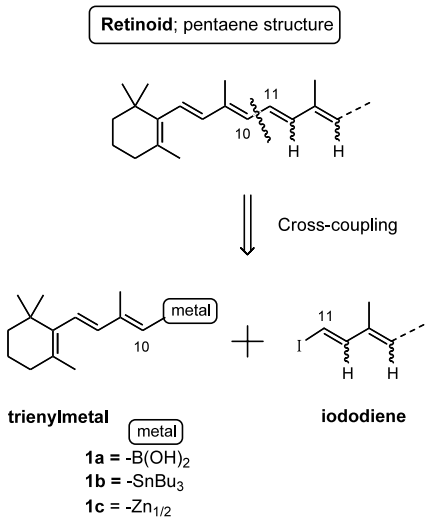
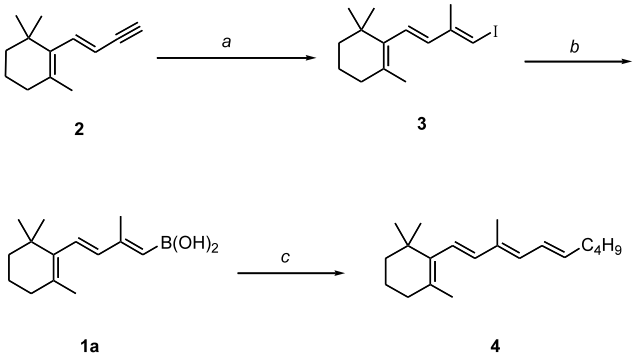
0040-4039/03/$ - see front matter
doi:10.1016/S0040-4039(03)00550-1



Scheme 1.



Scheme 2. *Reagents and conditions*: (a) i. $Bu_3SnMgMe$, cat. CuCN, THF then MeI; ii. iodine, CH_2Cl_2 or i. Cp_2ZrCl_2, $AlMe_3$, $ClCH_2CH_2Cl$ then iodine; (b) i. BuLi, −78°C, THF, ii. $B(OPr^i)_3$, −20°C, THF, rt, then purification by silica gel column chromatography; (c) i. (*E*)-1-iodohexene, cat. $Pd(PPh_3)_4$, aq. KOH, Ag_2CO_3, THF.

Stannylmagnesiation of enyne **2**[11] and quenching the resultant adduct with iodomethane gave trienylstannane **1b**. Immediate iodination of the crude extract gave trienyliodide **3** in 70% yield.[12] Lithium–iodine exchange of **3** with *n*-BuLi at −20°C and subsequent metal exchange with triisopropyl borate gave diisopropyl trienylborate, which was hydrolyzed by the usual work-up to give trienylboronic acid **1a**. Fortunately, this boronic acid can be purified by silica gel chromatography and is reasonably stable for storage in solution. However, drying-up of the solvent from the acid gave rise to decomposition and polymerization, resulting in rapid loss of its purity.[13] We recommended that **1a** is stored in solution. Subsequently, compound **1a** was subjected to coupling reaction with 1-iodohexene in the presence of $Pd(PPh_3)_4$ (5 mol%), KOH, and Ag_2CO_3 in THF at room temperature to give tetraene **4** in 53% yield.[14,15]

3. Synthesis of 13-aryl substituted (11*Z*)-retinal

In the recognition process of vision, the first photo-isomerization of the (11*Z*)-retinal chromophore induces structural change in the light receptor rhodopsin. The isomerization activates transmembrance G-protein-coupled receptor proteins for the signal communication path and the signal is eventually transmitted to the brain.[16] The static structure of rhodopsin has recently been revealed by X-ray crystallographic studies within a range of 3.3 Å level of resolution.[17] Although the three dimensional structure of static rhodopsin has been determined, the dynamic flexibility of opsin may allow it to take a modified (11*Z*)-retinal into a pocket of the protein hole. Such a loose interaction between a ligand and protein is sometimes observed depending on the size of the ligand as well as some other interactive forces between the ligand and protein.[18] We were interested in the case of 13-substituted analogues of (11*Z*)-retinal and opsin, and have attempted the synthesis of 13-aryl substituted (11*Z*)-retinal (Fig. 2).

The preparation of the other coupling unit, iododiene **9**, is outlined in Scheme 3. Stereoselective introduction of trimethylsilylacetylene to *O*-TBDPS protected 3,3-dibromo-2-propen-1-ol by Sonogashira coupling gave (*Z*)-bromoenyne **5** in 87% yield.[19] Suzuki coupling of **5** with phenylboronic acid in the presence of 5 mol% $PdCl_2$(dppf) and sodium carbonate in THF at 55°C gave (*E*)-enyne **6a** in 90% yield with retention of the configuration. The stereochemistry was confirmed by NOE that was observed between the CH_2 group and *ortho* protons of an aromatic ring. Deprotection of TMS group and of TBDPS ether by treatment with an excess of tetrabutylammonium fluoride gave **7a** in 86% yield. Then, iodination of terminal alkyne with iodine and morpholine in refluxing benzene gave iodoenyne **8a** in a quantitative yield. Finally, partial *cis* hydrogenation of the alkynyl bond with diimide[20] gave (2*Z*,4*Z*)-3-phenyl-5-iodopentadien-1-ol **9a** in 39% yield along with over reduced product and starting material. On the other hand, Suzuki coupling of **5** with *p*-formylbenzeneboronic acid followed by acetal formation gave **6b** in 79% yield in two steps. The same reaction sequences, desilylation, iodination and partial hydrogenation as those for the synthesis of **9a** gave **9b** in 64% yield in three steps (Scheme 4).

Pd-catalyzed cross-coupling of **1a** with iododienes **9a** and **9b** was conducted in THF at room temperature in the presence of silver carbonate and aq. KOH. The pentaenes **10a** and **10b** were obtained in 54 and 49% yields, respectively.[21] The observed coupling constant, 11.8 Hz, between C_{11}–H and C_{12}–H in both compounds

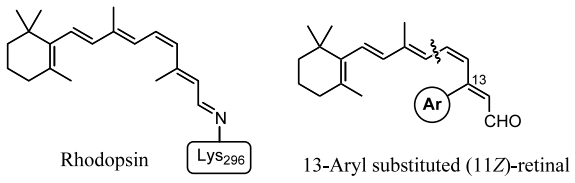
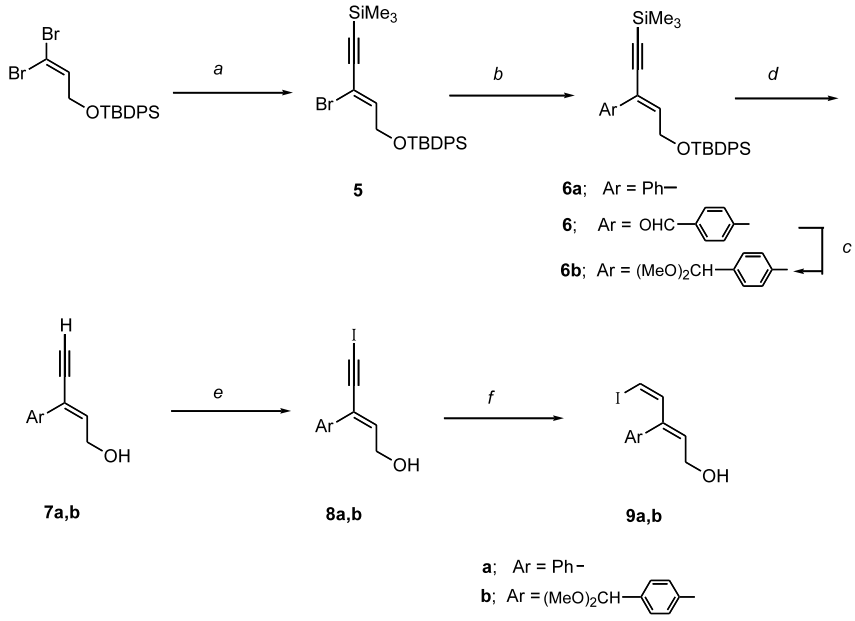
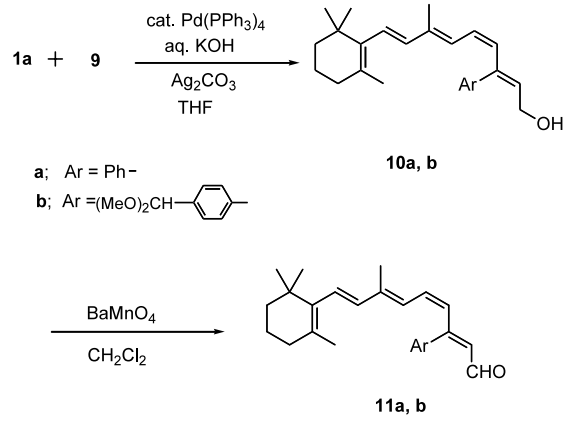


Figure 2.



Scheme 3. *Reagents and conditions*: (a) i. trimethylsilylacetylene, cat. $PdCl_2$(dppf), CuI, Pr^i_2NH, benzene; (b) $ArB(OH)_2$, cat. $PdCl_2$(dppf), Na_2CO_3, THF; (c) MeOH, cat. TsOH, $MgSO_4$; (d) TBAF, THF; (e) iodine, morpholine, benzene; (f) KOOCN=NCOOK, AcOH, THF.



Scheme 4.

clearly indicated a (11*Z*)-configuration. Finally, oxidation of **10a** by barium manganate in methylene chloride furnished the synthesis of geometrically pure retinal **11a**[21] in 30% yield. Similarly, **11b**[21] was obtained in 23% yield. These 13-aryl substituted derivatives were less stable than other (11*Z*)-retinals. During the oxidation and purification, they started decomposing gradually even when all of the operations were carried out under dark or red-colored lamp conditions.

In conclusion, we have described a novel and efficient method for the preparation of geometrically pure trienylboronic acid **1a** as an isolable alkenylmetal reagent, which is found to be a versatile unit for retinoid synthesis by Pd-catalyzed cross-coupling reaction. The first synthesis of 13-aryl substituted (11*Z*)-retinals was accomplished by this methodology.

Acknowledgements

This work was financially supported by the Grant-in-Aid for Scientific Research on Priority Areas (A) from the Ministry of Education, Science, Sports and Culture, Japan, and by a Special Grant from the Nagase Science and Technology Foundation.

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10. Stannylmagnesiation of enyne; Uenishi, J.; Kawahama, R.; Tanio, A.; Wakabayashi, S. *Chem. Commun*. **1993**, 1438–1439. After work-up and successive purification by silica gel column chromatography, hardly separable proto-destannylated product and reagent derived by-products were largely contaminated with trienylstannane. In addition, it was found that the cross-coupling of **1b** with **9** under the Stille conditions gave a mixture of geometric isomers at least by our hands.
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12. The compound **3** was also prepared by the Negishi's method using Cp_2ZrCl_2 and trimethylaluminum in the similar yield.
13. The yield of **1a** is estimated to be 60–70% approximately. Polymerization and/or protonation were observed during the decomposition process. An immediate use of **1a** is of course recommended. However, as long as it is kept in solution, the boronic acid is fairly stable during a day. When the acid can be stored in frozen benzene at −20°C, it survives at least for a week, but is gradually decomposed after a month. **Preparation of 1a**: To a mixture of iodotriene (1.0 mmol) in THF (5 ml) BuLi was added dropwise (1.6 M in hexane, 2.2 mmol) at −78°C, and the mixture was stirred for 10 min. After the reaction completed, triisopropyl borate (5 mmol) was added to the mixture and it was stirred for an additional 30 min at room temperature. After the mixture was diluted with hexane, the whole mixture was directly charged on silica gel column chromatography eluted by 20% EtOAc in hexane (R_f value of the boronic acid was 0.2 on silica gel TLC developed by 20% EtOAc in hexane). This boronic acid was used as THF solution in the next cross coupling reaction.
14. Compound **1a** was usually used 2–3 equiv. for iodoalkene.
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21. **10a**; oil; R_f=0.33 (40% Et_2O in hexane); ^1H NMR (300 MHz, C_6D_6) δ 7.24–7.05 (5H, m), 6.48 (1H, t, J=11.8 Hz), 6.26 (1H, d, J=16.1 Hz), 6.16 (1H, d, J=11.8 Hz), 6.12 (1H, d, J=11.8 Hz), 6.06 (1H, d, J=16.1 Hz), 5.98 (1H, t, J=6.8 Hz), 3.98 (2H, d, J=6.8 Hz), 1.96 (2H, t, J=6.2 Hz), 1.83 (3H, s), 1.75 (3H, s), 1.64–1.54 (2H, m), 1.51–1.45 (2H, m), 1.11 (6H, s). **10b**; oil; R_f=0.23 (40% Et_2O in hexane); ^1H NMR (300 MHz, C_6D_6) δ 7.54 (2H, d, J=8.4 Hz), 7.20 (2H, d, J=8.4 Hz), 6.48 (1H, t, J=11.8 Hz), 6.24 (1H, d, J=16.2 Hz), 6.16 (1H, d, J=11.8 Hz), 6.14 (1H, d, J=11.8 Hz), 6.02 (1H, d, J=16.2 Hz), 5.98 (1H, t, J=6.7 Hz), 5.41 (1H, s), 3.97 (2H, d J=6.7 Hz), 3.23 (6H, s), 1.95 (2H, t, J=6.1 Hz), 1.83 (3H, s), 1.73 (3H, s), 1.66–1.54 (2H, m), 1.51–1.44 (2H, m), 1.08 (6H, s). **11a**; oil; R_f=0.73 (40% Et_2O in hexane); ^1H NMR (300 MHz, C_6D_6) δ 9.73 (1H, d, J=8.1 Hz), 7.30–6.95 (5H, m), 6.51 (1H, t, J=12.1 Hz), 6.34 (1H, d, J=8.1 Hz), 6.29 (1H, d, J=15.8 Hz), 5.94 (1H, d, J=12.1 Hz), 5.89 (1H, d, J=15.8 Hz), 5.77 (1H, d, J=12.1 Hz), 1.94 (2H, t, J=5.8 Hz), 1.71 (3H, s), 1.68 (3H, s), 1.62–1.51 (2H, m), 1.49–1.41 (2H, m), 1.07 (6H, s). **11b**; oil; R_f=0.57 (40% Et_2O in hexane); ^1H NMR (300 MHz, C_6D_6) δ 9.73 (1H, d, J=8.1 Hz), 7.43 (2H, d, J=8.1 Hz), 7.06 (2H, d, J=8.1 Hz), 6.52 (1H, t, J=12.1 Hz), 6.35 (1H, d, J=8.1 Hz), 6.27 (1H, d, J=15.8 Hz), 5.94 (1H, d, J=12.1 Hz), 5.86 (1H, d, J=15.8 Hz), 5.81 (1H, d, J=12.1 Hz), 5.35 (1H, s), 3.19 (6H, s), 1.93 (2H, t, J=6.2 Hz), 1.71 (3H, s), 1.67 (3H, s), 1.63–1.50 (2H, m), 1.47–1.41 (2H, m), 1.04 (6H, s).