Caesium fluoride-promoted Stille coupling reaction: an efficient synthesis of 9*Z*-retinoic acid and its analogues using a practical building block†

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A highly efficient and rapid total synthesis of 9*Z*-retinoic acid was accomplished by caesium fluoride-promoted Stille coupling reaction; using a common building block, 9*Z*-retinoic acid analogues were also prepared by the same method without isomerisation of the *Z*-double bond.

Retinoid X receptors (RXRα, β, γ) belong to the nuclear receptor superfamily of eukaryotic transcription factors. RXRs modulate gene transcription through formation of homodimers (RXR–RXR) or heterodimers including RXR–RARs (retinoic acid receptors), RXR–LXRs (liver X receptors), RXR–PPARs (peroxisome proliferator-activated receptors), RXR–FXR (farnesoid X receptor), RXR–TR (thyroid receptor), and RXR–VDR (vitamin D receptor).[1] 9*Z*-Retinoic acid **1** and its synthetic analogues **2** bind to RXRs and regulate various biological functions such as cell differentiation, proliferation, and control of embryonic development.[2] Therefore, the development of an efficient synthetic route for **1** and its analogues **2** is desirable (Fig. 1).

The structure of **1** consists of a highly conjugated polyene with a partial *Z*-configuration of the double bond and a terminal carboxylic acid. Thus, **1** is a challenging synthetic target for organic chemists in view of its biological activity and unique structure. To date, several synthetic methods for **1** have been reported and were based on the Horner–Emmons reaction, Peterson reaction, Stille coupling reaction, and Suzuki coupling reaction.[3,4] To the best of our knowledge, the shortest synthesis of **1** was accomplished by de Lera *et al.* (four steps from 2,2,6-trimethylcyclohexanone, 48.5% overall yield) and its elegant convergent synthesis may be applied to 9*Z*-retinoic acid analogues' syntheses (Scheme 1).[4] However, a key step of this method includes the transformations of vinyl iodide **3** to its boronic ester **6** and of organostannane **4** to the corresponding iodide **7**, followed by condensation of both products by a Suzuki coupling reaction. These troublesome transformations were essential because the attempted Stille coupling reaction of vinyl iodide **3** with organostannane **4** failed due to its unreactivity and because of isomerisation of the *Z*-double bond of **5**. The poor outcome was attributed to the sterically hindered vinyl iodide **3** and electron-withdrawing group-substituted organostannane **4**. We reported the successful synthesis of **1** by the Stille coupling reaction of vinyl triflate

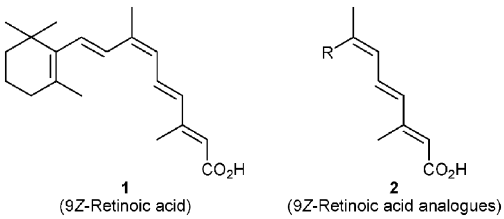
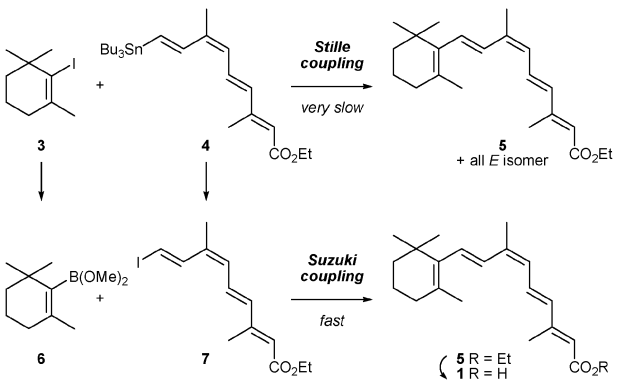


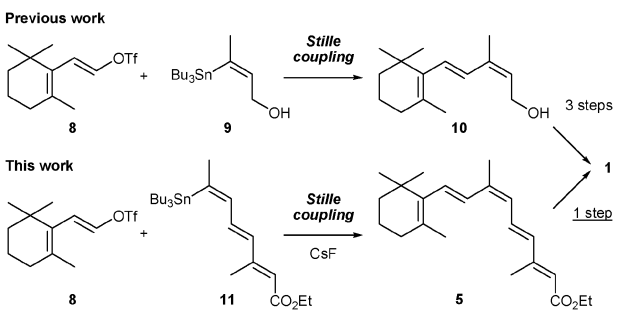
Fig. 1 9*Z*-Retinoic acid **1** and its synthetic analogues **2**.



Scheme 1 Reported synthetic route of **1**.

8 with stannanyl alcohol **9** (Scheme 2).[3c] However, this synthetic methodology was based on a linear synthesis, and is not suitable for the synthesis of a wider variety of analogues of **1**. Therefore, we sought an easier and more powerful coupling procedure for the convergent synthesis of **1**.

In this communication, we report an efficient, rapid synthesis of 9*Z*-retinoic acid **1** that includes the Stille coupling reaction of stannanyl ester **11**, which bears an electron-withdrawing group, as a key reaction (Scheme 2). The advantages of our method are: (1) stannanyl ester **11** can be prepared from commercially available 2-butyn-1-ol in only three steps in a large scale procedure; (2) the key Stille coupling reaction precludes the troublesome transformation by Suzuki coupling



Scheme 2 Our synthetic route of **1**.

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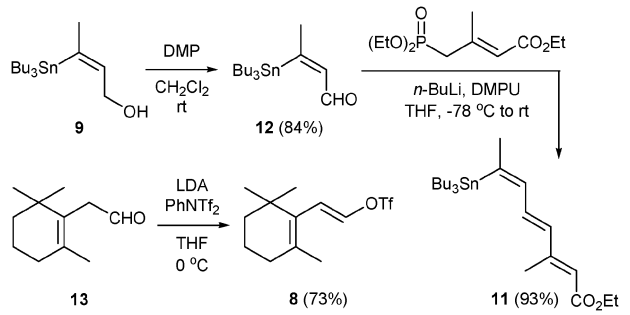


Scheme 3 Preparation of coupling components **11** and **8**.

as mentioned above; (3) the isomerisation of the *Z*-double bond does not occur in the reaction; and (4) our originally developed stannanyl ester **11** can serve as a practical building block in convergent syntheses leading to useful analogues.

Stannanyl ester **11** was prepared in three steps (Scheme 3). Treatment of 2-butyn-1-ol with Red-Al followed by Bu_3SnCl afforded *Z*-alcohol **9** in 93% yield,[5] which was transformed to *Z*-aldehyde **12** by Dess–Martin oxidation in 84% yield. Horner–Emmons reaction of **12** with phosphonate in the presence of 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) yielded **11** in 93% yield in a highly stereoselective manner, which was confirmed by various NMR spectra.

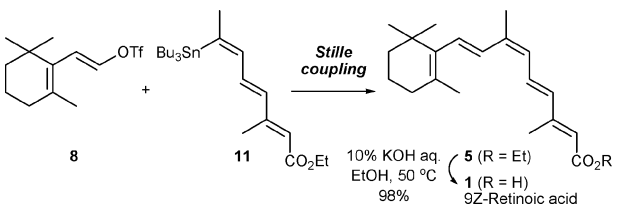
Next, another side coupling component, vinyl triflate **8**, was prepared in 73% yield and $E : Z = >98 : 2$ selection by the reaction of aldehyde **13** with LDA followed by reaction with *N*-phenyl-bis(trifluoromethanesulfonimide) ($PhNTf_2$). The use of KO*t*-Bu instead of LDA as a base decreased the observed stereoselectivity ($E : Z = 92 : 8$). The $E : Z$ ratios of **8** were determined by ^{1}H NMR spectra.

With stannanyl ester **11** and triflate **8** are in hand, optimisation of the Stille coupling reaction was carried out (Table 1). Our previous coupling conditions [$Pd_2(dba)_3{\cdot}CHCl_3$ (dba = dibenzylideneacetone), $AsPh_3$, DMF] yielded **5** in only 12% after 24 h (entry 1).[3c] This result is consistent with the previous finding that the Stille coupling reaction using organostannane with an electron-withdrawing group suffered from its poor reactivity and homo-coupling.[6] Next, we examined additives for promoting the Stille coupling (entries 2, 3).[7] To our surprise, the use of caesium fluoride (CsF) as an additive not only enhanced the reaction rate but also prevented the isomerisation of the *Z*-double bond (entries 3–5). Similar enhancement of reaction rate by CsF in Stille coupling is well known.[7b] All our trials using other fluoride sources such as TBAF did not indicate an efficient enhancement. Recently, Baldwin *et al*. reported that a combination of CuI and CsF significantly promoted the Stille coupling,[8] but these conditions did not favor the coupling reaction of **8** and **11** (entry 6). Therefore, the optimised reaction conditions were determined as in entry 5. Notably, the tin residues from the Stille coupling reaction mixture were removed completely by column chromatography using KF-silica as a stationary phase.[9]

The hydrolysis of ester **5** has already been reported by our group (10% KOH aq., EtOH, 50 °C, 98% yield)[3d] so we could accomplish the total synthesis of 9*Z*-retinoic acid **1** in three steps from aldehyde **13** in 63.0% overall yield or in four steps from *Z*-alcohol **9** in 67.4% overall yield. This 9*Z*-retinoic acid synthesis has the fewest number of steps and highest yield of all reported methods.

The powerful and convergent synthesis of **1** prompted us to prepare various analogues of **1**.[10] Thus, Stille coupling reactions of stannanyl ester **11** with other vinyl triflates **14a–j** were tried (Table 2). Nonconjugate vinyl triflate **14a** from (−)-menthone provided coupling product **15a** in good yield by our explored method (Method A). However, vinyl triflate **14b** from (+)-camphor did not afford coupling product **15b** by Method A. It is noteworthy that Baldwin's developed procedure (Method B) was also effective for the coupling reaction of **11**. Compound **15b** was obtained in good yield under these conditions, despite the lesser reactivity in the case of **8** and **11** (Table 1, entry 5). Therefore, the results in Table 2 were presented under the reaction conditions specified by either Method A or B. *O*- and *N*-Heterocyclic triflates **14c–d** may also be applied to our conditions to afford **15c–d** in moderate yields. Bicyclic triflates **14e–g** having an aromatic ring, were not successful with Method A, but were with Method B. The coupling reactions of vinyl triflates **14h–i** from sesquiterpenes proceeded to obtain **15h–i** in satisfactory yields. Finally, acyclic vinyl triflate **14j** derived from (−)-nopol was tried,

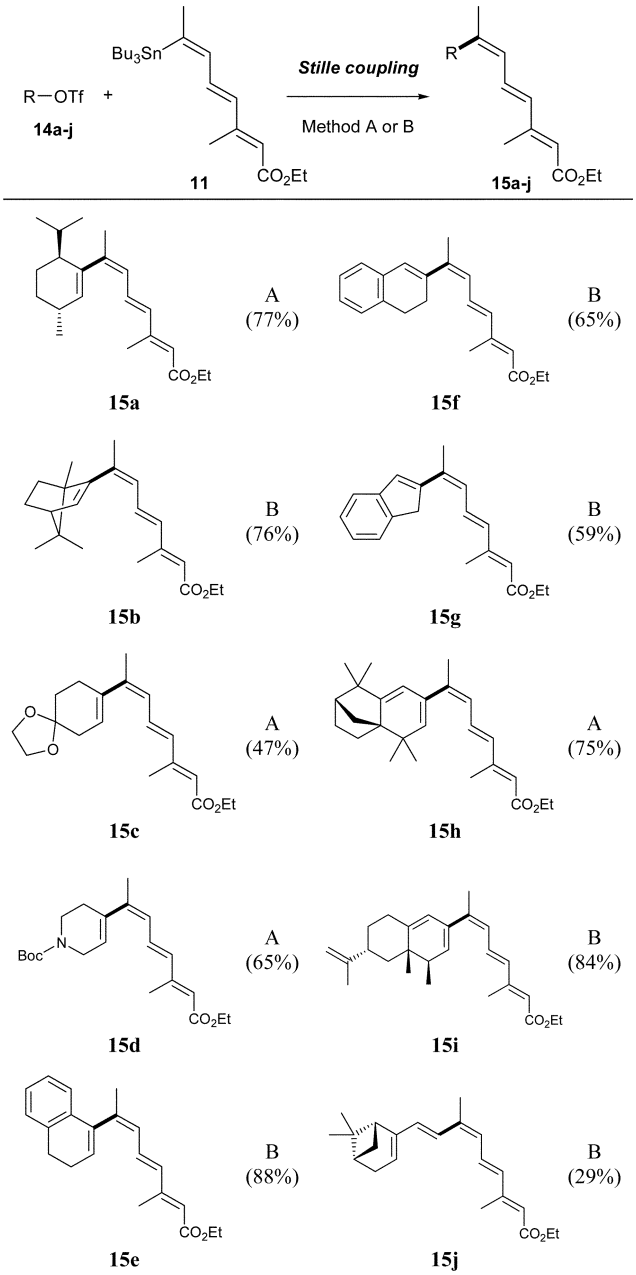
Table 1 Optimisation of the Stille coupling reaction of **11** and **8**[a]



Entry	Pd source (mol%)	Additive (mol%)	**8** : **11** (equiv.)	Time/h	**5** (%)
1	$Pd_2(dba)_3{\cdot}CHCl_3$ (2)	$AsPh_3$ (8)	1 : 1.3	24	12
2	$Pd_2(dba)_3{\cdot}CHCl_3$ (2)	$AsPh_3$ (8), LiCl (200)	1 : 1.3	24	13
3	$Pd_2(dba)_3{\cdot}CHCl_3$ (2)	$AsPh_3$ (8), CsF (200)	1 : 1.3	14	64
4	$Pd_2(dba)_3{\cdot}CHCl_3$ (4)	$AsPh_3$ (16), CsF (200)	1 : 1.1	12	74
5	$Pd_2(dba)_3{\cdot}CHCl_3$ (4)	$AsPh_3$ (16), CsF (200)	1.1 : 1	1.5	88
6	$Pd(PPh_3)_4$ (10)	CuI (20), CsF (200)	1 : 1.5	15	15

[a] All reactions were carried out in DMF at 40–45 °C.

Table 2 Stille coupling with stannyl ester **11**[a]



[a] Method A: **14** (1.1 equiv.), **11** (1.0 equiv.), $Pd_2(dba)_3{\cdot}CHCl_3$ (4 mol%), $AsPh_3$ (16 mol%), CsF (2.0 equiv.), DMF, 45 °C. Method B: **14** (1.0 equiv.), **11** (1.3 equiv.), $Pd(PPh_3)_4$ (10 mol%), CuI (20 mol%), CsF (2.0 equiv.), DMF, 45 °C.

but desired product **15j**, being unstable, was obtained in only low yield. The reactivity of the coupling reaction may depend on the structure of triflates **14a–j**, but no clear tendencies were observed. Nevertheless, Stille coupling of **11** would directly offer various 9*Z*-retinoic acid derivatives **15a–j** in a minimum number of steps.

In conclusion, we have developed the rapid synthesis of 9*Z*-retinoic acid **1**, and an efficient, convergent synthetic route to its analogues **15a–j** by Stille coupling using the common stannanyl ester **11**. Although electron-withdrawing group-substituted organostannane is generally known to be unreactive for Stille coupling, we demonstrated the enhancement effect of the reaction rate by CsF. This research would provide a new synthetic strategy for not only natural products but also highly conductive molecules in the field of materials sciences. Hydrolysis of esters **15a–j** to carboxylic acids, tests of their biological activity, and Stille coupling of **11** with other coupling partners, including aromatic halides and vinyl nonaflates,[11] are ongoing.

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Notes and references

1 V. Giguère, *Endocr. Rev.*, 1999, **20**, 689–725, and references cited therein.
2 (*a*) *The Retinoids: Biology, Chemistry and Medicine*, ed. M. B. Sporn, A. B. Roberts and D. S. Goodman, Raven, New York, 2nd edn, 1993; (*b*) R. A. Heyman, D. J. Mangelsdorf, J. A. Dyck, R. B. Stein, G. Eichele, R. M. Evans and C. Thaller, *Cell*, 1992, **68**, 397–406; (*c*) W. K. Hong and M. B. Sporn, *Science*, 1997, **278**, 1073–1077.
3 (*a*) Y. L. Bennani, *J. Org. Chem.*, 1996, **61**, 3542–3544; (*b*) A. Wada, S. Hiraishi, N. Takamura, T. Date, K. Aoe and M. Ito, *J. Org. Chem.*, 1997, **62**, 4343–4348; (*c*) A. Wada, Y. Nomoto, K. Tano, E. Yamashita and M. Ito, *Chem. Pharm. Bull.*, 2000, **48**, 1391–1394; (*d*) A. Wada, K. Fukunaga, M. Ito, Y. Mizuguchi, K. Nakagawa and T. Okano, *Bioorg. Med. Chem.*, 2004, **12**, 3931–3942.
4 (*a*) Y. Pazos, B. Iglesias and A. R. de Lera, *J. Org. Chem.*, 2001, **66**, 8483–8489; (*b*) Y. Pazos and A. R. de Lera, *Tetrahedron Lett.*, 1999, **40**, 8287–8290.
5 D. L. Aubele, S. Wan and P. E. Floreancig, *Angew. Chem., Int. Ed.*, 2005, **44**, 3485–3488.
6 E. Piers, P. L. Gladstone, J. G. K. Yee and E. J. McEachern, *Tetrahedron*, 1998, **54**, 10609–10626.
7 LiCl promotes the oxidative addition and CsF facilitates the transmetallation in the Stille coupling reaction, see: (*a*) W. J. Scott and J. K. Stille, *J. Am. Chem. Soc.*, 1986, **108**, 3033–3040; (*b*) A. G. Martínez, J. O. Barcina, C. A. de Fresno and L. R. Subramanian, *Synlett*, 1994, 1047–1048.
8 (*a*) S. P. H. Mee, V. Lee and J. K. Baldwin, *Chem.–Eur. J.*, 2005, **11**, 3294–3308; (*b*) S. P. H. Mee, V. Lee and J. K. Baldwin, *Angew. Chem., Int. Ed.*, 2004, **43**, 1132–1136.
9 D. C. Harrowven and I. L. Guy, *Chem. Commun.*, 2004, 1968–1969.
10 Syntheses of 9*Z*-retinoic acid analogues, see: (*a*) A. Wada, Y. Mizuguchi, H. Miyake, M. Niihara, M. Ito, K. Nakagawa and T. Okano, *Lett. Drug Des. Discovery*, 2007, **4**, 442–445; (*b*) A. Wada, Y. Mizuguchi, M. Shinmen, M. Ito, K. Nakagawa and T. Okano, *Lett. Drug Des. Discovery*, 2006, **3**, 118–122; (*c*) B. H. Lipshutz, G. C. Clososki, W. Chrisman, D. W. Chung, D. B. Ball and J. Howell, *Org. Lett.*, 2005, **7**, 4561–4564; (*d*) B. Domínguez, Y. Pazos and A. R. de Lera, *J. Org. Chem.*, 2000, **65**, 5917–5925; (*e*) ref. 3*c*, 3*d* and 4.
11 For a review of nonaflate, see: (*a*) K. Ritter, *Synthesis*, 1993, 735; For a recent example of Stille coupling of vinyl nonaflate, see: (*b*) A. Wada, Y. Ieki, S. Nakamura and M. Ito, *Synthesis*, 2005, 1581–1588.

