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LETTERS

Total synthesis of (±)-8′-trifluoromethyl abscisic acid

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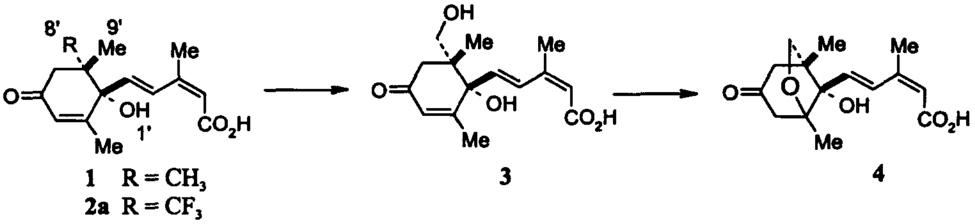
Abstract

While 8′-trifluoromethyl ABA (**2a**) was known to be one of the most active and stable analogs tested in assays for ABA-like activity, a thorough evaluation of its biological properties was limited by compound availability. The current synthesis, which includes the preparation of a previously unknown key intermediate 2-methyl-2-trifluoromethyl-1,4-cyclohexanedione-mono ethylene ketal (**18**), has been accomplished in 14 steps and 3% yield. The key fluorinated ketal intermediate **18** was prepared in six steps and 20% yield. © 1999 Published by Elsevier Science Ltd. All rights reserved.

Abscisic acid (ABA, **1**) is a widely distributed plant hormone in higher plants that is involved in such processes as abscission of leaves, stomatal closure, seed germination, senescence and dormancy.[1] However, instability greatly limits its efficacy as a plant growth regulator or herbicide.[2] The most important process for metabolizing ABA (**1**) in planta is via hydroxylation of the 8′-methyl substituent which leads to phaseic acid (**4**) (Scheme 1).[3] Circumventing this rapid breakdown, such as blocking oxidation with a trifluoromethyl group in the case of **2a**, has been applied to dramatically improve biological activity. However, the only known synthesis of **2a** with published experimentals was prohibitive (23 steps with <1% overall yield).[4] We sought to devise a synthesis by which we could prepare multi-gram quantities of this material.



Scheme 1.

There were several key problems in preparing the 8-CF3 analog of ABA. The primary problem was that of establishing the stereochemistry of the 1′-hydroxyl relative to the 8′-substituent (see structure 1

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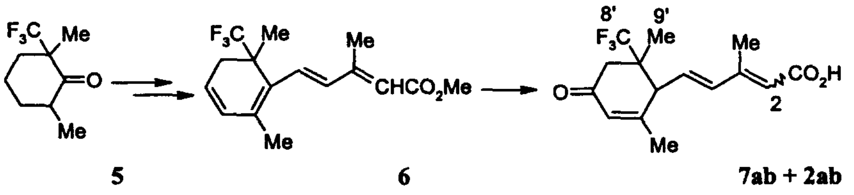
for numbering system). In general, the biological activity of 8′-derivatized analogs has been far more interesting than the analogous 9′-diastereomers.[5] The premier method for establishing the correct *syn* stereochemistry has been via conjugate addition of a Grignard reagent to an enone, where the 8′-R group is directed in via the 1′-hydroxyl group to ensure the proper stereochemistry. In our case, this was not practical because with the exception of organocadmium reagents,[6] trifluoromethyl organometallic reagents that are reactive are difficult to form and to work with, and they generally do not add 1,4 to enones.[7]

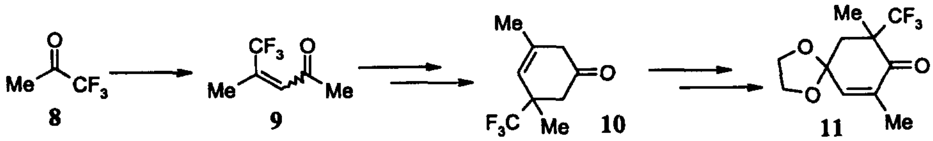
Another problem was establishing the stereochemistry of the dienoic acid. It was known that the thermodynamically preferred isomer is of the *E,E*-configuration, which is *not* the natural or active geometry (which is *E,Z*).[8] The landmark synthesis of Hirai (Scheme 2) suffered from poor control of either of the aforementioned problems, giving a 1:14 mixture of the desired 8′-CF_3 diastereomer bearing the *E,Z*-tail, with respect to the other three possible undesirable variations. The photosensitized oxidation used to install the appropriate oxidation states gave the thermodynamically favored stereoisomers, which were not the desired isomers.



1 : 2 ratio 2-*Z* / 2-*E*
1 : 4 ratio 8'/9'-CF_3
5% desired isomer
(1 : 2 : 4 : 8)

Scheme 2.

An alternative synthesis of **2a** was reported by Kim et al. in 1995.[9] This synthesis, which hinged on addition of an acetylide to fluorinated isophorone 4-mono-ethylene ketal **11**, was attractive owing to its relative convergence and brevity (13 steps overall). The Kim synthesis (Scheme 3) prepared intermediate **11** from trifluoroacetone in seven steps (22% yield). Unfortunately, experimental details were not published.

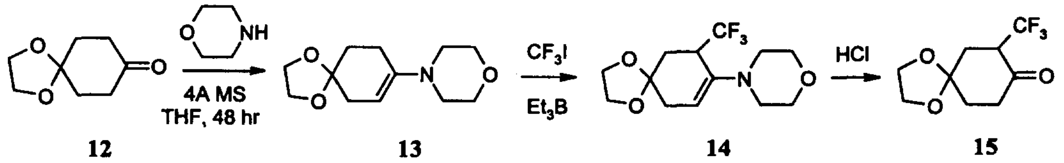


Scheme 3.

Thus, we decided to pursue our own approach to enone **11**, and thereafter utilize the acetylide addition sequence previously reported by both Kim et al.[9] and Abrams et al.[5] Stereoselectivity for the alkynyllithium addition favors the desired isomer as the acetylide adds to the carbonyl of **11** from the opposite side of the sterically and electronically influential trifluoromethyl group,[10] making the trifluoromethyl group and the newly formed hydroxyl group *syn* to one another.

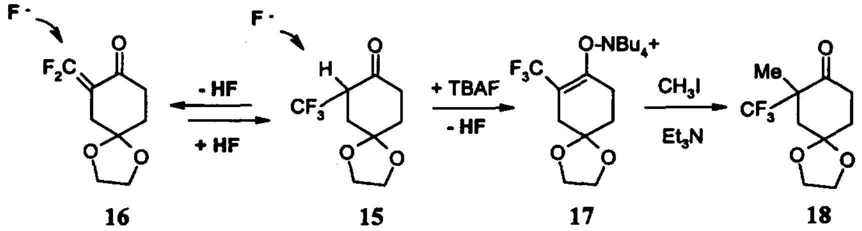
We envisioned key intermediate **11** to be derived from the commercially available cyclohexanedione monoketal **12**. The primary concern in our sequence was introduction of the trifluoromethyl group. Of the electrophilic trifluoromethylating agents tried,[11] none were effective at alkylating the enolate of 1,4-cyclohexanedione mono-ethylene ketal. Not until we began investigating radical methods for introducing this group did we achieve some success.

The 1,4-cyclohexanedione mono-ethylene ketal (**12**) was converted to its morpholine enamine **13** (Scheme 4).[12] The enamine **13** was then subjected to a flow of gaseous iodotrifluoromethane in the presence of triethylamine and a catalytic amount of triethylborane as a radical initiator.[6c] This novel free radical trifluoromethylation[13] consistently and reproducibly produced the monotrifluoromethylated enamine product **14**, which has been isolated and characterized as the isomer shown. Hydrolysis with dilute HCl gave the monotrifluoromethylated ketone **15**, which crystallized from the reaction mixture rendering further purification unnecessary. On a 0.16 mole scale, the overall one-pot yield was 45–50% based on **12**.



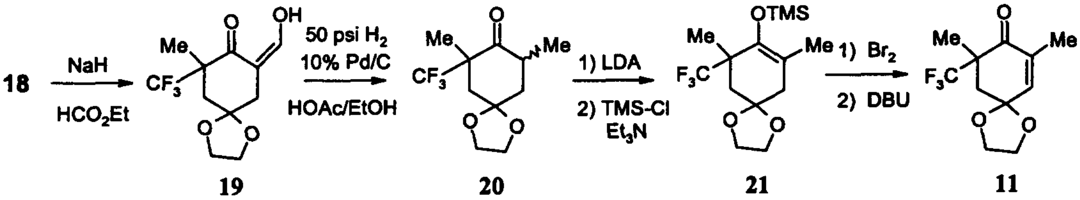
Scheme 4.

Introduction of one or both of the required methyl groups would have been most conveniently performed upon enamine **14**. However, this compound did not react with iodomethane under standard enamine alkylation conditions. Thus, we were forced to contend with the possibility that enolization of **15** would cause elimination of fluoride to give the reactive enone **16** (Scheme 5), which could decompose further. The use of standard enolizing bases indeed resulted only in decomposition. We felt that addition of a fluoride source would shift the equilibrium in favor of enolate **17**. Using two equivalents of tetrabutylammonium fluoride to function both as a base and to prevent elimination of HF, we were able to isolate a 60% yield of the mono-alkylated ketone **18**.[14] Apparently, the activating influence of the trifluoromethyl group was enough to differentiate the two enolizable positions: only regioisomer **18** was formed. Inclusion of bases such as sodium hydride or sodium methoxide led to multiple alkylated products which proved to be difficult to separate.



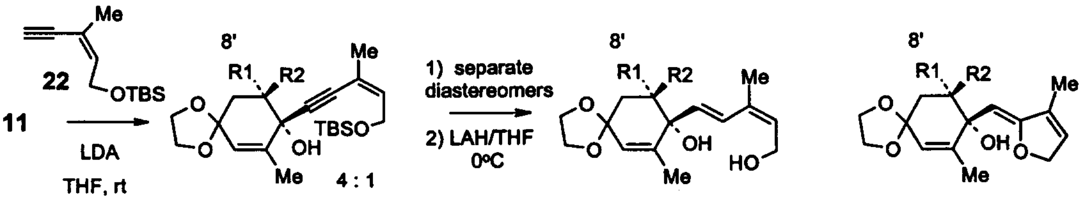
Scheme 5.

Mono-alkylation of the unsubstituted methylene was achieved by formylation of ketone **18** to give β-keto aldehyde **19** followed by catalytic hydrogenation to give **20**[15] in 70% yield as a 3:1 mixture of diastereomers (Scheme 6).[16] Insertion of the α,β-unsaturation to give **11** was achieved with excellent conversion (95% based on recovered starting material **20**) by preparation of the enolsilane **21** of ketone **20**, then treatment with one equivalent of bromine followed by dehydrobromination using the method of Abrams and Rose.[17] Attempts to install the unsaturation using sulfoxide or selenoxide elimination were not as clean.



Scheme 6.

Introduction of the commercially available tail **22** to our key intermediate enone **11** was achieved by 1,2-addition of a lithium acetylide to enone **11** (Scheme 7). The favored stereoisomer was determined to be the desired isomer **23a** by NOE and by comparison with the literature.[9,18] This was consistent with attack of the acetylide on the least hindered face and away from the electron rich trifluoromethyl group. Stereoselectivity was affected by reaction temperature: a 4:1 ratio of **23a**:**23b** (8′ to 9′) was obtained at room temperature while lower temperatures increased formation of the 9′ isomer **23b**. These diastereomers were easily separable at this point by either normal-phase or reversed-phase chromatography, and each diastereomer was carried on individually to final products **2a** and **2b** for comparison with authentic material and physical data reported in the literature.[2]



23a $R^1 = CF_3, R^2 = Me$
b $R^1 = Me, R^2 = CF_3$

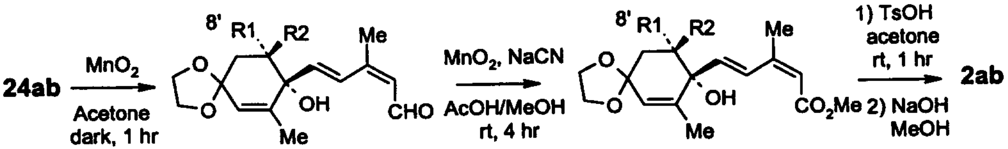
24a $R^1 = CF_3, R^2 = Me$
b $R^1 = Me, R^2 = CF_3$

25

Scheme 7.

One-pot reduction/desilylation of the propargyl alcohol with lithium aluminum hydride[19] rather than with the previously reported use of RedAl®[5] improved the yield of **24a** from 5% to 21%. The major byproduct was furan **25**, which appeared to be formed by competitive cyclization of the desilylated vinylogous propargyl alcohol.

Due to questionable stability of the intermediates, the final transformations were performed without purification. The oxidations of the allylic alcohol were best carried out sequentially using MnO_2 (Scheme 8). Despite the appearance of complete and clean conversion of precursor to products **26** and **27** in each case, the mass balance was poor for these reactions upon removal of the MnO_2 by filtration down a short plug of Celite (50% recovery). Removal of the ethylene ketal with acid and saponification of the ester gave the desired products **2a** and **2b** (91–95% yield from **27**).



26a $R^1 = CF_3, R^2 = Me$
b $R^1 = Me, R^2 = CF_3$

27a $R^1 = CF_3, R^2 = Me$
b $R^1 = Me, R^2 = CF_3$

Scheme 8.

Acknowledgements

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14. Compound **18**: MS (EI) *m/z* for $C_{10}H_{13}O_3F_3$=239 (M+1), 181 (base). 300 MHz ^1H NMR ($CDCl_3$, ppm) 4.10–3.95 (m, 4H), 2.92–2.79 (m, 1H), 2.48–2.27 (m, 2H), 2.08–1.96 (m, 3H), 1.54 (s, 3H). 75 MHz ^{13}C NMR (^1H decoupled, $CDCl_3$, ppm) 201.3, 126.0 (q, J=281 Hz), 106.4, 64.9, 64.3, 53.0 (q, J=21 Hz), 39.4, 35.8, 33.8, 18.8. 282 MHz ^{19}F NMR (^1H decoupled, $CDCl_3$, ppm) −71.7.
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16. As the stereochemistry is lost in the next step, the major product was not identified.
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18. Compound **23a**: MS (EI) *m/z* for $C_{23}H_{35}O_4F_3Si$=331 (M-OTBS); parent not observed. 300 MHz ^1H NMR ($CDCl_3$, ppm) 5.83 (qt, 1H, J=6.2 Hz, 1.5 Hz), 5.46–5.45 (m, 1H), 4.36–4.32 (m, 2H), 4.03–3.91 (m, 4H), 2.48–2.43 (m, 1H), 1.98 (d, 3H, J=1.1 Hz), 1.95–1.90 (m, 1H), 1.87 (q, 3H, J=1.5 Hz), 1.39 (s, 3H), 0.91–0.89 (m, 9H), 0.10 (s, 6H). 282 MHz ^{19}F NMR (^1H decoupled, $CDCl_3$, ppm) −72.8.
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