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First total synthesis of tuberonic acid

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Abstract—A vinyl group as an acetic acid side chain was attached to the optically active monoacetate of 4-cyclopentene-1,3-diol with CH_2=CHMgBr, LiCl, and a CuCN catalyst to produce the S_N2-type product, from which the full carbon skeleton of tuberonic acid was constructed through Mitsunobu inversion, Claisen rearrangement, and Wittig reaction. At the last stage, the THP protective group was removed with $MgBr_2$ in Et_2O. The diastereomeric ratio of tuberonic acid and the trans isomer was 92:8 by ^{1}H NMR spectroscopy.

Depicted in Figure 1 are some of the α-linolenic acid metabolites, which regulate important events of plants.[1] The common structural features of these metabolites are the cis orientation of the two side chains on the ring and attachment of the pentenyl chain to the α position of the carbonyl group. Consequently, the metabolites in general tend to undergo epimerization to the more stable trans isomers. In fact, there have been reports that describe the isolation of the trans isomers.[2]

The instability mentioned above and the existence of the acid moiety have restricted reactions and reagents to be used for the synthesis of these metabolites. In fact, *epi*-jasmonic acid (**1**) was only synthesized as a mixture with the lactone,[3] while methyl *epi*-jasmonate biosynthesized from *epi*-jasmonic acid by the carboxyl methyltransferase[4] has been synthesized by several groups[3,5] probably due to its neutral property as an ester form. On the other hand, we have established the synthesis of metabolites with a long acid chain such as 12-oxo-PDA and OPC-8:0 starting with the monoacetate of 4-cyclopentene-1,3-diol (**4** in Scheme 1), to which the C(1)–C(8) chain was attached by using the highly S_N2 directing reagent system of RMgCl/CuCN (cat.).[6] With 12-oxo-PDA Howe has characterized the enzymes for the β-oxidation,[7] and Ohta elucidated the specific

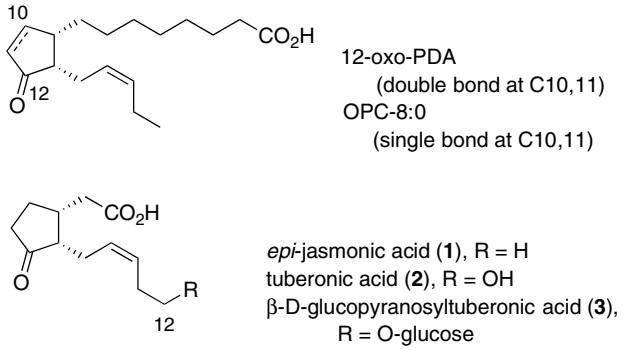
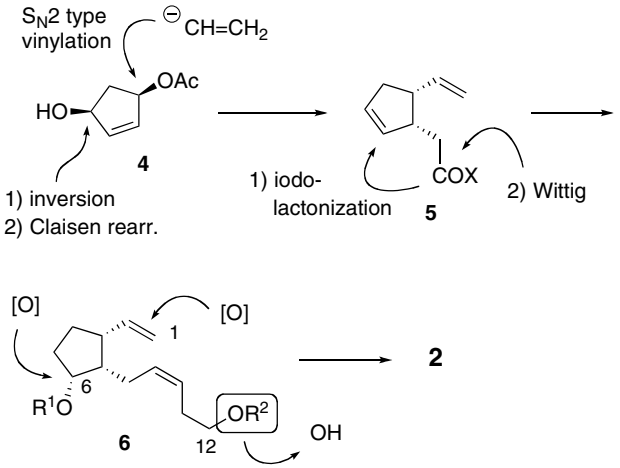


Figure 1. Some of the metabolites of linolenic acid.



Scheme 1. An approach to tuberonic acid.

Keywords: Tuberonic acid; Total synthesis; Stereoselective; Monoacetate of 4-cyclopentene-1,3-diol.
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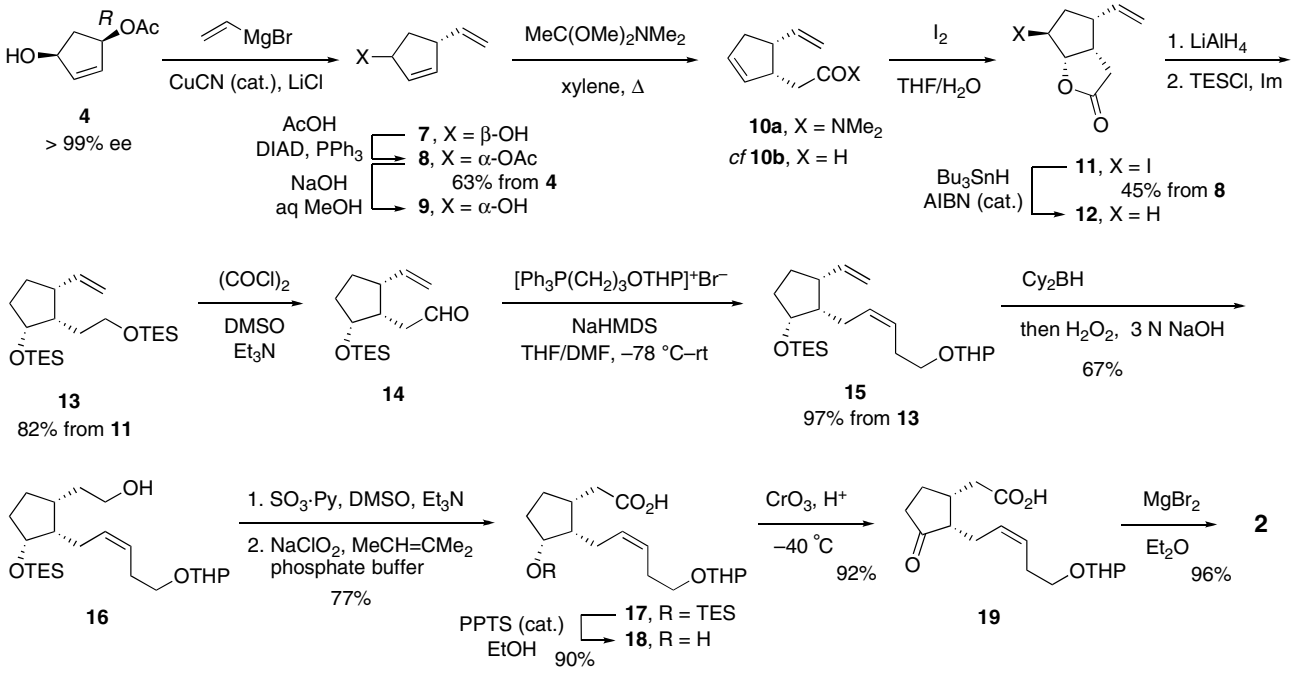
DNA induced by 12-oxo-PDA.[8] These studies strongly suggest that other metabolites should possess their own biological role(s) in plants.

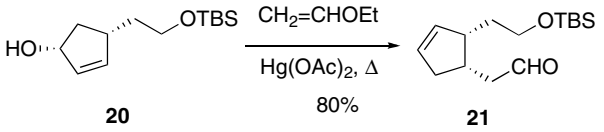
With the above implication in mind, we have been interested in the synthesis of tuberonic acid (**2**). This molecule is a natural product as such[9] and an aglycone of β-D-glucopyranosyltuberonic acid (**3**),[10] both of which are isolated from the leaves of potato as tuber-forming substances.[11] Previously, synthesis of the trans isomer of **2** in the racemic form has been reported[12] while the methyl ester of **2** in an optically active and a racemic form has been reported by Kitahara[13] and Kiyota,[14] respectively. In the last step, the CF_3CO (TFA) and TMS protective groups of the hydroxyl group at C12 have been removed under mild conditions without epimerization (in MeOH at rt; HFpyridine at −40 °C). However, due to their unstable nature even under slightly acidic and basic conditions, these groups are incompatible with transformations of the standard class. On the other hand, the authors have mentioned that the unwanted epimerization took place with deprotection of the more stable THP, EE, and TBDPS protective groups in 70% AcOH[13] or with HF.[14]

With the limited positive information for an epimerization-free approach to acid **2**, we decided, as presented in Scheme 1, to apply our strategy[6,15] developed for the synthesis of 12-oxo-PDA and OPC-8:0 in order (1) to construct the full carbon framework as **6** with minimum effort starting with monoacetate **4** through **5**; (2) to concentrate much time upon oxidative manipulation of **6** at C1 (to COOH) and C6 (to C=O) and thereafter unmasking of the OR^2 group at C12 without the epimerization. We found that the THP group meets the criterion of this approach. Herein, we present the results along this line and the first total synthesis of tuberonic acid.

The first step of our synthesis is CuCN-catalyzed vinylation of (1*R*)-acetate **4** (>99% ee by chiral HPLC analysis) with CH_2=$CHMgBr$ in the presence of LiCl (Scheme 2), which afforded **7** with a high regioselectivity (93:7) and complete stereoselectivity.[16,17] This vinyl group was chosen as a $-CH_2CO_2H$ equivalent.[18] Without purification due to the volatile property, the hydroxyl group of **7** was inverted by using the Mitsunobu reaction with AcOH and DIAD. Acetate **8** obtained in a 63% yield from **4** was free of the stereoisomer, that is, the acetate of **7**, by 300 MHz ^1H NMR analysis (**8**, δ 3.21–3.32; acetate of **7**, δ 3.40–3.52). Hydrolysis of **8** afforded alcohol **9**, which was subjected to Claisen rearrangement under the standard conditions (excess CH_2=CHOEt, $Hg(OAc)_2$ (cat.), benzene, 180–200 °C, 60 h). However, the reaction was slow to produce the corresponding aldehyde **10b** only in a 22% yield with the recovered alcohol. Coordination of the terminal olefin to the mercury catalyst is a likely reason for the low yield because Claisen rearrangement of alcohol **20** under the same conditions produced aldehyde **21** in an 80% yield (Eq. 1). Alternatively, we investigated an Eschenmoser variant,[19] which was performed simply by heating a xylene solution of alcohol **9** and $MeC(OMe)_2NMe_2$ under reflux for 1 h to afford amide **10a**. Without purification the amide was subjected to iodolactonization with I_2 in aqueous THF to produce iodolactone **11** in a 45% yield from acetate **8**. The iodo group was then removed with Bu_3SnH and AIBN to produce lactone **12**[20] without participation of the olefin moiety in the reaction.



Scheme 2. Synthesis of tuberonic acid (**2**).



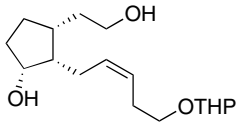
20 **21** (1)

In the synthesis of 12-oxo-PDA and OPC-8:0,[6a] the lactone carbonyl moiety was converted to the aldehyde through a four-step sequence of (i) HO^-; (ii) CH_2N_2; (iii) TESCl; (iv) DIBAL, in which the products of steps i and ii were isolated and semi-purified as fast as possible to prevent lactonization back to **12**. In the present study, we investigated another sequence of reactions involving direct conversion of a primary $TESOCH_2$ moiety to an aldehyde group by Swern oxidation.[21] Thus, the reduction of lactone **12** with $LiAlH_4$ followed by bissilylation afforded **13** in an 82% yield from iodolactone **11**. Swern oxidation of **13** proceeded selectively at the primary carbon to afford aldehyde **14**, which could be used for the next Wittig reaction without chromatographic purification. As expected, the intermediates in this shorter sequence (three-step) were chemically quite stable to allow easy handling.

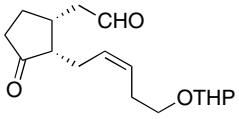
Two phosphonium salts **22a**,**b** with different protective groups (R^2 = PMB (*p*-$MeOC_6H_4CH_2$), THP) were conceived as a Wittig partner of **14**. Among them, **22a** with the PMB group was eliminated due to the reason found in a preliminary study using a model acid derived from racemic methyl jasmonate.[22]

$[Ph_3P(CH_2)_3OR^2]^+Br^-$ **22** for R^2; **a**, PMB; **b**, THP

The crude aldehyde **14** (vide supra) upon Wittig reaction with the anion derived from the THP ether **22b** and NaHMDS ($NaN(TMS)_2$) afforded olefin **15**[20] (= **6** with R^1 = TES; R^2 = THP in Scheme 1) stereoselectively in a high yield. Hydroboration of **15** with Cy_2BH (Cy: *c*-C_6H_{11}) followed by oxidative workup produced alcohol **16**, which upon oxidation first with SO_3·pyridine and then with $NaClO_2$ under neutral conditions[23] afforded acid **17** in a 52% yield from olefin **15**. Selective removal of the TES group in **17** was accomplished under two conditions with PPTS (0.3 equiv) in EtOH (rt, 1 h) and with TBAF (6 equiv) in THF (rt, 4 h) to produce alcohol **18**[20] in 90% and 71% yields, respectively. Jones oxidation of alcohol **18** at −40 °C was successful in several runs to produce **19** without any injury to the THP group or epimerization to the trans isomer.[24] Unsuccessfully attempted accesses to **19** are as follows. Jones oxidation of alcohol **23** derived from **16** at temperatures of −40 to −30 °C afforded a mixture of products. On the other hand, PCC oxidation of **23** followed by Jones oxidation of the resulting keto-aldehyde **24** at >−30 °C gave a mixture. On the contrary, no oxidation of **24** took place at −40 °C (cf. successful oxidation of **18** at −40 °C). Another attempted oxidation of aldehyde **24** with $NaClO_2$ furnished a 70:30 mixture of **19** and the trans isomer.



23



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After unsuccessful deprotection of the THP group of **19** under various conditions,[25] we found that $MgBr_2$ (3 equiv) in Et_2O[26] at room temperature for 2 h provided **2** in high yield with minimum epimerization (**2** over the trans isomer = 92:8 by ^1H NMR spectroscopy).[20]

Time-dependency of the epimerization of tuberonic acid (**2**) was studied at room temperature in CD_3OD with a 90:10 mixture of **2** and the trans isomer by monitoring the protons for **2** and the trans isomer.[24] In contrast to the fairly rapid epimerization under the acidic conditions,[25] detectable epimerization was not observed for over 21 days! On the other hand, epimerization took place, but slowly, in the presence of K_2CO_3 (heterogeneous in CD_3OD) to produce a 40:60 mixture after 7 days. Now, scientists working in this area are free of the fear of autoepimerization by its own acidity that was suggested by Kiyota et al.[14]

In summary, we have established for the first time a method for obtaining tuberonic acid (**2**), which was of a 92% purity over the trans isomer. Furthermore, we confirmed the stable nature of **2** under neutral conditions over an extended period. The stability established herein will be quite informative for modifying the isolation of **2** in future, and thus facilitate research in this field.

Acknowledgments

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17. In the absence of LiCl, the S_N2 product **7** and anti S_N2' isomer was produced in a ratio of 63:37.
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20. $[\alpha]_D$, ^{1}H NMR (300 MHz, $CDCl_3$ or CD_3OD), and/or ^{13}C NMR (75 MHz, $CDCl_3$) data of the intermediates. Compound **12**: ^{1}H NMR ($CDCl_3$) δ 1.39–1.58 (m, 1H), 1.62–1.80 (m, 2H), 1.99 (dd, $J = 13$, 7 Hz, 1H), 2.36 (dd, $J = 19$, 5 Hz, 1H), 2.43 (dd, $J = 19$, 10.5 Hz, 1H), 2.53–2.67 (m, 1H), 2.90–3.03 (m, 1H), 4.95–5.03 (m, 1H), 5.01 (dt, $J = 17$, 1.5 Hz, 1H), 5.08 (dt, $J = 11$, 1.5 Hz, 1H), 5.71 (ddd, $J = 17$, 11, 6.5 Hz, 1H); ^{13}C NMR δ 26.9 (+), 29.7 (+), 32.7 (+), 40.9 (−), 46.1 (−), 85.8 (−), 116.7 (+), 136.9 (−), 177.7 (+). Compound **15**: ^{1}H NMR ($CDCl_3$) δ 0.59 (q, $J = 8$ Hz, 6H), 0.95 (t, $J = 8$ Hz, 9H), 1.43–1.92 (m, 11H), 1.88–2.21 (m, 2H), 2.35 (q, $J = 7$ Hz, 2H), 2.59 (dq, $J = 17$, 4 Hz, 1H), 3.40 (dt, $J = 9$, 7 Hz, 1H), 3.44–3.55 (m, 1H), 3.72 (dt, $J = 9$, 7 Hz, 1H), 3.87 (ddd, $J = 11$, 7.5, 3.5 Hz, 1H), 4.15–4.22 (m, 1H), 4.57–4.63 (m, 1H), 4.80–4.91 (m, 2H), 5.30–5.58 (m, 2H), 5.93 (dt, $J = 17$, 10 Hz, 1H); ^{13}C NMR δ 5.0 (+), 7.0 (−), 19.6 (+), 24.1 (+), 25.6 (+), 28.2 (+), 30.0 (+), 30.8 (+), 34.6 (+), 45.5 (−), 50.0 (−), 62.3 (+), 67.1 (+), 75.3 (−), 98.7 (−), 113.1 (+), 125.4 (−), 131.6 (−), 143.2 (−). Compound **18**: ^{1}H NMR ($CDCl_3$) δ 1.4–2.8 (m, 19H), 3.34–3.58 (m, 2H), 3.73–3.94 (m, 2H), 4.10–4.24 (m, 1H), 4.55–4.66 (m, 1H), 5.34–5.60 (m, 2H); ^{13}C NMR δ 19.5 (+) and 19.6 (+), 23.5 (+) and 23.6 (+), 25.4 (+), 28.1 (+), 29.8 (+) and 30.0 (+), 30.36 (+) and 30.45 (+), 33.2 (+) and 33.3 (+), 36.46 (−) and 36.52 (−), 36.8 (+), 47.7 (−), 62.3 (+) and 62.6 (+), 67.0 (+) and 67.4 (+), 73.9 (−), 99.0 (−) and 99.5 (−), 127.4 (−), 130.5 (−) and 130.7 (−), 179.4 (+). Compound **19**: $[\alpha]_D^{27}$ +10 (*c* 1.43, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.3–2.6 (m, 17H), 2.78–2.93 (m, 1H), 3.35–3.58 (m, 2H), 3.67–3.95 (m, 2H), 4.56–4.66 (m, 1H), 5.32–5.62 (m, 2H); ^{13}C NMR δ 19.6 and 19.7, 23.16 and 23.21, 25.5, 25.90 and 25.93, 28.1 and 28.2, 30.7 and 30.8, 34.1, 35.39 and 35.44, 35.6 and 35.7, 52.6, 62.4 and 62.6, 66.8 and 67.1, 98.8 and 99.0, 99.2, 127.8 and 128.0, 128.2 and 128.3, 177.0 and 177.1, 218.9. Compound **2**: $[\alpha]_D^{25}$ +11 (*c* 0.26, MeOH); ^{1}H NMR (300 MHz, CD_3OD) δ 1.77–1.95 (m, 1H), 1.9–2.5 (m, 10H), 2.74–2.88 (m, 1H), 3.55 (t, $J = 7$ Hz, 2H), 5.37–5.62 (m, 2H).
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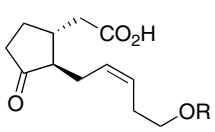
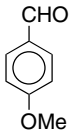
22. Deprotection of **i** proceeded as usual. However, separation of the products (alcohol **ii** and aldehyde **iii**) by chromatography on silica gel was unsuccessful due to the close mobility.



i, R = PMB
ii, R = H



iii

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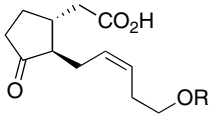
24. Upon alkaline treatment in aqueous MeOH, acids **19** and **2** underwent epimerization to trans isomers **iv** and **v**, respectively. The diagnostic signals for **19**, **iv**, **2**, and **v** in the ^{1}H NMR spectra (300 MHz, the former two in $CDCl_3$ and the latter two in CD_3OD) are (δ): **19**, 2.78–2.93; **iv**, 2.54–2.73; **2**, 2.74–2.88; **v**, 2.60–2.71 ppm. In addition, the ^{1}H NMR spectrum of **v** was consistent with that reported.[10c]



iv, R = THP
v, R = H

25. For example, deprotection with HCl (cat.) in MeOH at room temperature produced a 27:73 mixture of **2** and the trans isomer in an 81% yield.
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