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Synthesis of (±)-mispyric acid, a triterpene inhibitor of DNA polymerase β isolated from *Mischocarpus pyriformis*

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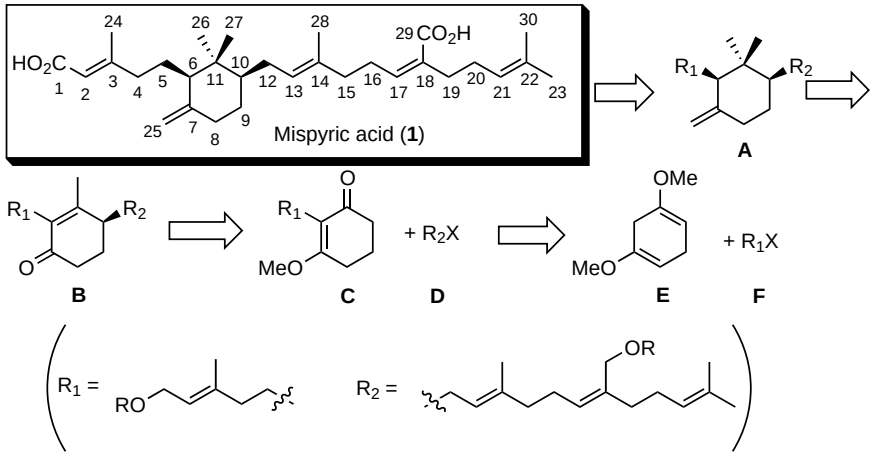
Abstract—The first synthesis of (±)-mispyric acid, an inhibitor of DNA polymerase β with a novel triterpene skeleton, was achieved by starting from isoprene, geraniol and 1,5-dimethoxy-1,4-cyclohexadiene.

In 1999, Hecht and co-workers isolated mispyric acid (**1**), a structurally unique triterpene dicarboxylic acid with a novel skeleton, from stem bark of Australian plant *Mischocarpus pyriformis* as a DNA polymerase β inhibitor.[1] This structurally unique monocyclic triterpene is presumably derived via a new biogenetic pathway including direct coupling of two farnesyl units.[1] In continuation of our works on synthesis of DNA polymerase inhibitors[2] and biosynthetically unique triterpenoids,[3] we initiated the synthesis of mispyric acid (**1**). Herein we report the first synthesis of (±)-**1**.

Our synthetic plan for (±)-**1** is shown in Scheme 1. The target compound **1** is readily obtainable from **A**, which may be prepared from **B** by Michael addition of a methyl group to the enone and subsequent methylenation of the carbonyl group. Our early studies, however, have shown that this Michael addition is quite difficult to achieve due to steric hindrance.[4] Cyclopropanation–reduction methodology is therefore to be adopted to overcome this difficulty. For the construction of the key intermediate **B**, two alkylations (**C** with **D**, and **E** with **F**) are chosen as key steps. Preparation of the two alkylating agents (**D** and **F**), corresponding to side chains, is considered to be possible by conventional methods.



Scheme 1. Structure of mispyric acid (**1**) and synthetic plan for (±)-**1**.

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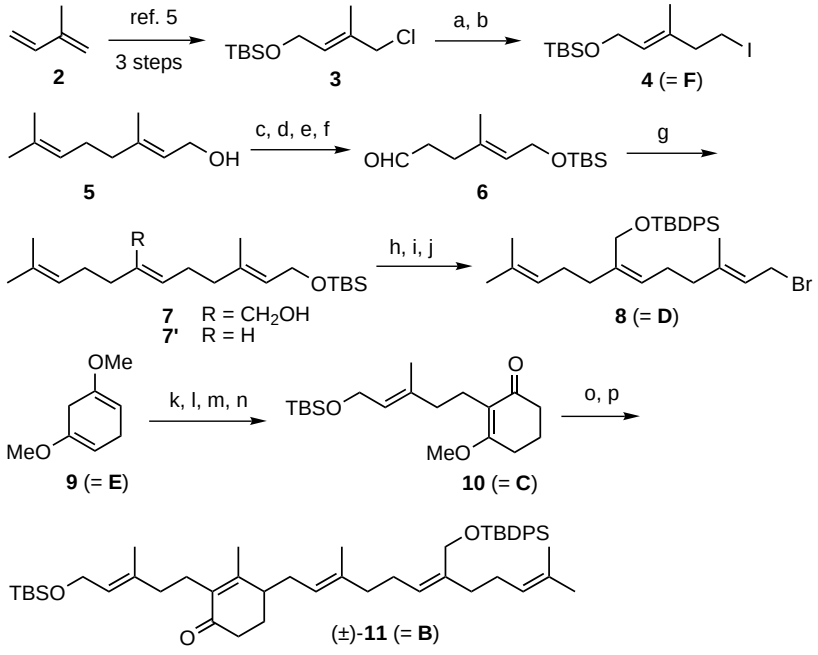
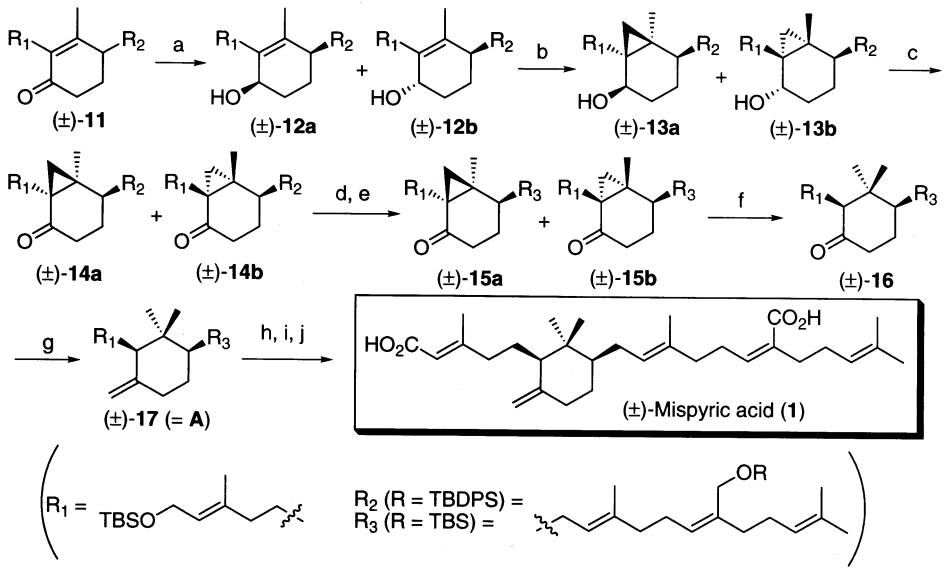
Our synthetic route to the key intermediate **B** (=**11**) is illustrated in Scheme 2. First, we synthesized the two alkylating agents as follows. According to the reported procedure, allylic chloride **3** was prepared from isoprene **2** in three steps.[5] The chloride **3** was converted to the corresponding bromide, which was exposed to the homologation reaction developed by Knochel et al.,[6] furnishing homoallylic iodide **4** (43% in two steps). It should be noted that this homologation was not successful with the allylic chloride **3**. Next, geraniol **5** was converted to aldehyde **6** in four steps (41%); TBS protection, regioselective epoxidation, oxidative cleavage of the epoxide and re-protection with TBSCl. The aldehyde **6** was then subjected to Corey–Yamamoto's modified Wittig reaction with concomitant hydroxymethylation.[7] In spite of all our efforts, the reaction of **6** with 5-methyl-4-hexenylidenetriphenylphosphorane[8] and paraformaldehyde gave adduct **7** in rather low yield. The major product (30% yield) of this reaction was **7′** without the hydroxymethyl group. However, we could obtain geometrically pure **7** without contamination of the undesired (*E*)-isomer. Although other methodologies[9] might be applicable for the preparation of **7**, this route was adopted due to its brevity. After protection of the hydroxy group of **7** as TBDPS ether (14% based on **6**), the resulting product was converted to the corresponding allylic bromide **8** in two steps (80%).

With two alkylating agents (**4** and **8**) in hand, we turned to construct the basic framework of mispyric acid. The lithiated 1,5-dimethoxy-1,4-cyclohexadiene **9**[10] was treated with **4** to give the alkylation product (75%), which was then converted to **10** in conventional three steps (41%); treatment with acid, enol ether formation and TBS protection. Alkylation of **10** with **8** was followed by treatment with MeMgBr and subsequent acidic work-up to furnish the key intermediate **11** (83% in two steps).

As mentioned in the synthetic plan, cyclopropanation–reduction methodology[11] was adopted for the addition of a methyl group to **11**, because our initial attempts with Michael addition met with failure. The key intermediate **11** was reduced under Luche's conditions[12] to give a mixture of two diastereomeric alcohols **12a**/**b** (98%, ratio=ca. 2:1). The structures of major and minor isomers were elucidated to be **12a** and **12b**, respectively, based on the similarity of ^{1}H NMR data between **12a**/**b** and the structurally related compounds.[13] Although these two diastereomers were separable, we used them as a mixture, because there was no need of separation for the synthesis of (±)-**1**. This diastereomeric mixture was then subjected to cyclopropanation[14] to furnish a mixture of **13a** and **13b** (94%),[15] which was immediately oxidized with PDC to afford a mixture of **14a** and **14b** (86%). At this stage, two different protecting groups (TBS and TBDPS) were converged to TBS in two steps (quant.), because the TBDPS group with two phenyl groups was not appropriate for the next dissolving metal reduction. Reductive cleavage of cyclopropane-ring[16] was performed under the classical Birch conditions (Li, NH_3, THF, *t*-BuOH) to yield the desired **16** (56%) as a single



Scheme 2. Synthesis of the key intermediate **11**. *Reagents and conditions*: (a) NaBr, DMF, rt; (b) ICH_2ZnI, CuI, LiI, THF, −25°C to rt (43% in two steps); (c) TBSCl, imidazole, DMF (98%); (d) *m*CPBA, $CHCl_3$ (81%); (e) $HIO_4{\cdot}2H_2O$, THF/H_2O; (f) TBSCl, imidazole, DMF (52% in two steps); (g) 5-methyl-4-hexenylidenetriphenylphosphorane, THF, −78°C; *s*-BuLi, −78°C; then $(CH_2O)_n$, 0°C to rt; (h) TBDPSCl, imidazole, DMF (14%, from **6**); (i) AcOH, H_2O, THF (92%); (j) PBr_3, pyridine, Et_2O (87%); (k) *t*-BuLi, THF, −78°C; then HMPA, **4**, (75%); (l) 1 M HCl, THF; (m) CH_2N_2, Et_2O/MeOH, 0°C; (n) TBSCl, imidazole, DMF (41% in three steps); (o) LDA, THF, −78°C; then **8**, −90°C to rt (93%); (p) MeMgBr, THF, 5°C to rt; then NH_4Cl aq. (89%).



Scheme 3. Synthesis of (±)-**1**. *Reagents and conditions*: (a) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH (98%); (b) CH_2I_2, Et_2Zn, Et_2O (94%); (c) PDC, MS 4A, CH_2Cl_2 (86%); (d) TBAF, THF (e) TBSCl, imidazole, DMF (quant. in two steps); (f) Li, NH_3, THF, *t*-BuOH, −78°C (56%); (g) $Ph_3P{=}CH_2$, THF, 0°C to rt (72%); (h) TBAF, THF (97%); (i) PDC, MS 4A, CH_2Cl_2; (j) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH, H_2O (31% in two steps).

isomer.[17] The ketone **16** was then exposed to Wittig methylenation to give **17** (72%). After removal of two TBS groups (97%), the resulting diol was oxidized stepwise to give the target compound (±)-**1** (31%, two steps) (Scheme 3). The various spectral data of synthetic (±)-mispyric acid (**1**) are in good accord with those of the natural product.[18]

In conclusion, the first synthesis of (±)-mispyric acid (**1**) was accomplished by starting from isoprene (**2**), geraniol (**5**) and 1,5-dimethoxy-1,4-cyclohexadiene (**9**). Further optimization of each step and the enantioselective version for the synthesis of **1** are now in progress.

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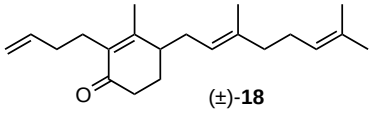
4. Michael addition was attempted using the model compound **18** as a substrate under various conditions as follows: Me_2CuLi-TMSCl-TMEDA, Me_2CuLi-Me_2S-Et_2O, Me_2Zn-$Ni(acac)_2$, Me_3Al-$Ni(acac)_2$, etc. The observed best yield was less than 20%.



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15. It was observed that the chromatographically purified **12a** gave **13a** as a single product by the cyclopropanation reaction.
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17. Unexpectedly and fortunately, the undesired *trans*-isomer could not be obtained.
18. Properties of synthetic (±)-**1**: colorless oil; IR ν_{max} (film) 3500–2500 (s, O–H), 1690 (s, C=O), 1640 (s, C=C) cm^{-1}; EIMS (*m*/*z*) 470, 452, 434, 419, 383, 365, 303, 285, 243, 235, 217, 203, 189, 175, 161, 147, 135, 121, 107, 93, 81,

69; HREIMS obsd. 470.3394 calcd. for $C_{30}H_{46}O_4$ 470.3396; ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 0.58$ (3H, s, 26-H_3), 1.03 (3H, s, 27-H_3), 1.12 (1H, m, 9-H), 1.20 (1H, m, 10-H), 1.58 (3H, s, 28-H_3), 1.59 (3H, s, 30-H_3), 1.59–1.67 (3H, m, 5-,6-,12-H), 1.68 (3H, s, 23-H_3), 1.69–1.78 (2H, m, 5-,9-H), 1.89 (1H, m, 8-H), 1.98-2.08 (2H, m, 15-H_2), 2.08–2.16 (3H, m, 4-H_2, 12-H), 2.17 (3H, br s, 24-H_3), 2.22–2.39 (5H, m, 8-H, 19-,20-H_2), 2.61 (2H, q, $J = 7.3$Hz, 16-H_2), 4.51 (1H, s, 25-H), 4.86 (1H, s, 25-H), 5.06–5.16 (2H, m, 13-,21-H), 5.68 (1H, s, 2-H), 6.00 (1H, t, $J = 7.3$ Hz, 17-H); ^{13}C NMR (100 MHz, $CDCl_3$) $\delta =$ 15.1, 16.1, 17.7, 19.2, 22.8, 25.7, 26.6, 27.8, 28.1, 29.1, 30.2, 34.6, 37.4, 39.2, 39.6, 40.0, 48.6, 53.0, 106.5, 114.8, 123.4, 125.3, 130.5, 132.3, 134.5, 145.6, 148.5, 164.0, 171.7, 173.0.