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First Total Synthesis of (±)-Methyl Gummiferolate Using a Homoallyl–Homoallyl Radical Rearrangement Reaction

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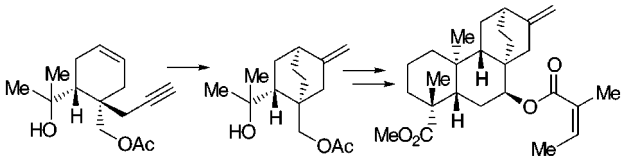
ABSTRACT

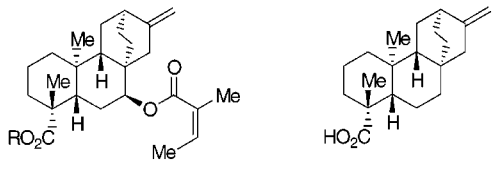


(±)-Methyl gummiferolate

The first total synthesis of (±)-methyl gummiferolate (1b) has been achieved with a high diastereoselectivity. The key steps included the homoallyl–homoallyl radical rearrangement reaction of the enyne 8 to afford the suitably functionalized bicyclo[2.2.2]octane 9 and the intramolecular Diels–Alder reaction of the tetraene 12 for the construction of the AB ring system of 1b.

Gummiferolic acid (**1a**), isolated from *Margotia gummifera* by Pinar et al.,[1] is a tetracyclic diterpene which possesses a bicyclo[2.2.2]octane subunit in the CD ring part and an angeloxy group attached to C-7 in the B ring. Although little is known about the substantial biological activity of atisirenoic acid (**2**),[2] **1a** shows plant growth-regulatory activity similar to or greater than that displayed by gibberellic acid.[3] Judging from the result of the bioassay, the presence of an oxygenated function on C-7 is important, as it increases the activity. In addition, gummiferolic acid (**1a**) has been used as an invaluable substrate in the field of microbiological transformation.[4] The unique structural characteristics and the promising biological activities have made gummiferolic acid (**1a**) an attractive synthetic target.

We have investigated the synthetic potential of the homoallyl−homoallyl radical rearrangement reaction[5] and recently reported a sequential three-step, one-pot construction of the bicyclo[2.2.2]octane ring system controlled by the stereoelectronic effect of the substituent group.[6] In this paper, we wish to present the first total synthesis of (±)-methyl gummiferolate (**1b**), in which the homoallyl−homoallyl radical rearrangement reaction for the construction of the highly functionalized bicyclo[2.2.2]octane compound is employed as a key step.



Gummiferolic acid (**1a**); R=H
Methyl gummiferolate (**1b**); R=Me

Atisirenic acid (**2**)

Figure 1.

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(3) Villalobos, N.; Martin, L.; Macias, M. J.; Mancheno, B.; Grade, M. *Phytochemistry* **1994**, *37*, 635.
(4) (a) Fraga, B. M.; Guillermo, R. *Phytochemistry* **1987**, *26*, 2521. (b) Fraga, B. M.; Guillermo, R.; Hanson, J. R. *Phytochemistry* **1992**, *31*, 503.

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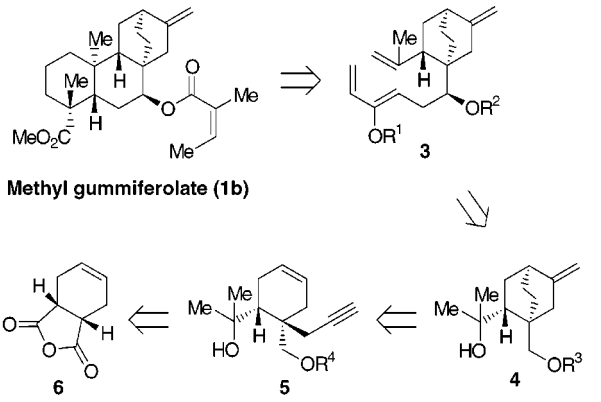
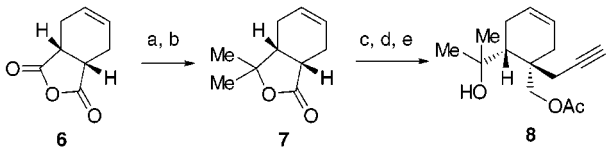
Scheme 1



As shown for the retrosynthetic analysis in Scheme 1, the key feature of the synthesis involves the intramolecular Diels−Alder reaction of the tetraene **3**, which would be prepared from the bicyclo[2.2.2]octane compound **4**. The bicyclic compound **4** would be produced by the homoallyl−homoallyl radical rearrangement reaction of the monocyclic enyne **5**, which could be derived from commercially available *cis*-1,2,3,6-tetrahydrophthalic anhydride (**6**).

The synthesis commenced with the transformation of **6** into lactone **7** in two steps by a modification of the known procedure (Scheme 2).[7] Introduction of a propargyl moiety

Scheme 2



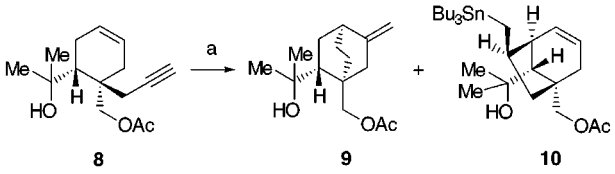
Reagents and conditions: (a) MeOH, reflux, 100%; (b) MeMgI, Et_2O, then aq. H_2SO_4, 76%; (c) LDA, THF, HMPA, −78 °C, then propargyl bromide, −78 °C, 85%; (d) LAH, Et_2O, 99%; (e) Ac_2O, pyridine, 100%.

to **7** followed by LAH reduction gave the corresponding diol, which was subjected to monoacetylation to afford the enyne **8** in 84% overall yield from **7**.

The homoallyl−homoallyl radical rearrangement reaction[8] of **8** provided the desired bicyclo[2.2.2]octane derivative **9**[9] in 32% yield. The bicyclo[3.2.1]octane compound **10**[9] (50%) was also generated (Scheme 3).

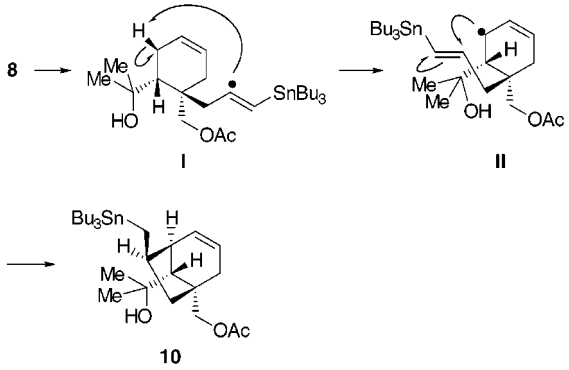
Formation of **10** from the enyne **8** may be interpreted by 1,5-radical translocation (**I** → **II**) of the initially formed vinyl radical **I** followed by a 5-*exo*-*trig* cyclization process as depicted in Scheme 4. On the basis of our model studies,[6]

Scheme 3



Reagents and conditions: (a) Bu_3SnH, AIBN, benzene, reflux, then SiO_2, CH_2Cl_2, **9**: 32%, **10**: 50%.

Scheme 4



the generation of the bicyclo[3.2.1]octane ring system was not anticipated.

Having assembled the requisite skeletal framework, the tetraene **12** for the next key step was synthesized as shown in Scheme 5. The isopropenyl moiety (dienophile) was prepared by the treatment of **9** with $POCl_3$ (99%), and the diene unit was constructed by hydrolysis followed by Parikh oxidation and coupling reaction with ((triethylsiloxy)penta-

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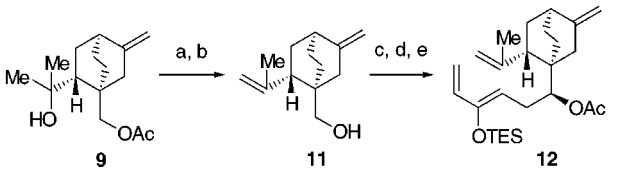
(8) **Procedure for the Conversion of 8 into 9**: To a stirred solution of the enyne **8** (19.7 g, 78.9 mmol) in degassed benzene (1.20 L) was slowly added a degassed benzene solution (40 mL) of Bu_3SnH (24.2 mL, 190 mmol) and AIBN (400 mg, 2.44 mmol) over a period of 2 h under reflux. After 2 h of refluxing, the solvent was removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (1.20 L), and then silica gel (300 g) was added. After vigorous stirring for 2 days, the mixture was filtered through Celite. The filtrate was concentrated to give an oil, which was chromatographed on silica gel. Elution with hexane followed by a 3:1 mixture of hexanes−EtOAc successively afforded the bicyclo[3.2.1]octane compound **10** (21.4 g, 50%) and **9**, containing a small amount of tin species. After washing of the crude **9** with hexane, the bicyclo[2.2.2]octane compound **9** (6.38 g, 32%), mp 67−69 °C, was isolated.

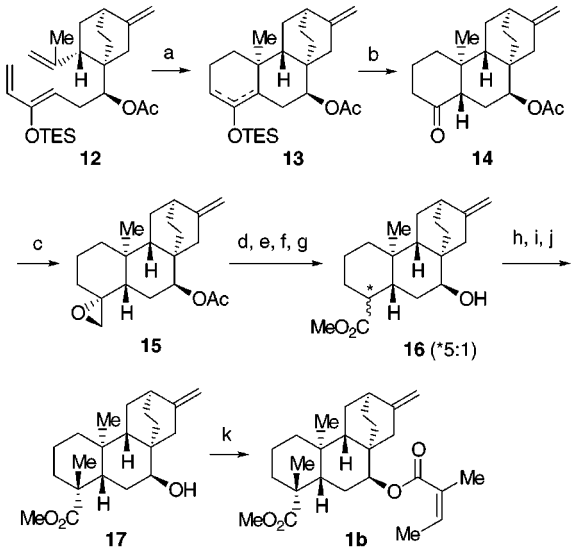
(9) The structure assigned to **10** is supported by a $^1H-^1H$ COSY experiment in the NMR spectrum. **Compound 9**: ^1H NMR (300 MHz, $CDCl_3$) δ 4.77 (1H, q, J = 2.0 Hz), 4.63 (1H, q, J = 2.0 Hz), 4.21 (1H, d, J = 11.0 Hz), 4.12 (1H, d, 11.0 Hz), 2.32−2.27 (1H, m), 2.26−2.10 (2H, m), 2.07 (3H, s), 1.94−1.73 (3H, m), 1.72−1.58 (3H, m), 1.43−1.33 (1H, m), 1.32 (3H, s), 1.26 (1H, ddd, J = 11.0, 9.0 and 2.0 Hz) and 1.18 (3H, s); ^{13}C (75 MHz, $CDCl_3$) δ 171.03, 150.63, 105.66, 74.78, 70.50, 49.24, 41.73, 37.73, 36.29, 32.59, 31.57, 26.09, 24.24, 23.87 and 20.94; MS (*m*/*z*): 234 ($M^+ - H_2O$). Anal. Calcd for $C_{15}H_{24}O_3$: C, 71.39; H, 9.58. Found: C, 71.22; H, 9.39. **Compound 10**: ^1H NMR (300 MHz, C_6D_6) δ 5.92−5.82 (1H, m), 5.38 (1H, dt, J = 9.0 and 3.0 Hz), 4.32 (2H, s), 2.51 (1H, dq, J = 17.0 and 2.0 Hz), 2.18 (1H, dq, J = 8.0 and 4.0 Hz), 2.04 (1H, dd, J = 6.0 and 3.0 Hz), 1.98 (1H, d, J = 3.0 Hz), 1.92−1.83 (2H, m), 1.75 (3H, s), 1.74 (1H, ddd, J = 17.0, 4.0 and 2.0 Hz), 1.63−1.51 (6H, m), 1.45−1.30 (7H, m), 1.28 (3H, s), 1.27 (3H, s), 1.00−0.80 (16H, m), 0.56−0.44 (1H, br s); HRMS calcd for $C_{27}H_{50}O_3{}^{120}Sn$ 542.2785, found 542.2799.

Scheme 5



Reagents and conditions: (a) $POCl_3$, pyridine, 99%; (b) K_2CO_3, MeOH, 100%; (c) DMSO, SO_3•pyridine, Et_3N, CH_2Cl_2, 97%; (d) 3-triethylsilyloxy-1,4-pentadiene, ^{s}BuLi, THF, –78 °C, 64% (+ minor stereoisomer 21%); (e) Ac_2O, DMAP, CH_2Cl_2, 99%.

Scheme 6



Reagents and conditions: (a) 200 °C, toluene, sealed tube, 99%; (b) Bu_4NF, THF, 88%; (c) $Me_3S^+OI^-$, NaH, DMSO, 50 °C, 73%; (d) BF_3•Et_2O, toluene, –20 °C; (e) $NaClO_2$, KH_2PO_4, 2-methyl-2-butene, ^{t}BuOH-H_2O; (f) DBU, MeI, MeCN; (g) K_2CO_3, MeOH, 50 °C, 65% for 4 steps; (h) TMSOTf, lutidine, CH_2Cl_2, 96%; (i) LDA, THF, –78 °C, then HMPA, MeI, –78 °C, 81%; (j) Bu_4NF, THF, 91%; (k) angelic acid, 2,4,6-trichlorobenzoyl chloride, Et_3N, toluene, 80 °C, 55%.

dienyl)lithium according to Oppolzer's method.[10] The stereochemical outcome of this coupling process can be explained by a Cram model. Finally, acetylation of the resulting hydroxyl group furnished the tetraene **12**.

Intramolecular Diels−Alder reaction of **12** provided a near-quantitative yield of the tetracyclic silyl enol ether **13**, which was rapidly treated with tetrabutylammonium fluoride to give the ketone **14** (88%) as the only observed product. The stereoselective protonation is presumably subject to thermodynamic control. Functionalization at the C-4 position proved to be much more difficult than expected. Ultimately, we adopted BF_3-promoted rearrangement of the exocyclic methylene epoxide.[11] A Corey−Chaykovsky reaction[12] of the ketone **14** led to the epoxide **15** (73%) with a high degree of stereoselectivity via attack from the face opposite to the angular methyl group at C-10. Acid-catalyzed rearrangement of **15** followed by oxidation, esterification, and hydrolysis of the acetyl moiety afforded the ester **16** in 65% overall yield. After protection of the hydroxyl group of **16**, methylation and deprotection of the silyl group yielded the alcohol **17** as a single product. Finally, the angelate ester group was prepared by applying Greene's technique (Scheme 6).[13] The synthetic (±)-methyl gummiferolate (**1b**) thus obtained was spectroscopically identical with that reported.[1]

In summary, the first total synthesis of (±)-methyl gummiferolate (**1b**) has been accomplished from commercially available *cis*-1,2,3,6-tetrahydrophthalic anhydride. The homoallyl−homoallyl radical rearrangement reaction-intramolecular Diels−Alder strategy should be adaptable for the synthesis of other atisirene-type terpenoids.

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