Natural Product Synthesis

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Total Synthesis of (−)-Samaderine Y from (*S*)-(+)-Carvone**

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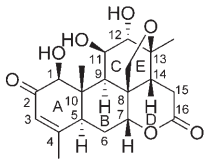
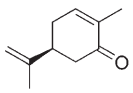
Quassinoids, a group of heavily oxygenated terpenoid bitter compounds isolated from the *Simaroubaceae* plant family, display a wide range of biological activities[1] and have attracted interest with respect to their synthesis during the past decades.[2] (−)-Samaderine Y (**1**), a pentacyclic quassinoid isolated from *Quassia indica*, was shown to exhibit in



(−)-samaderine Y (**1**)



(*S*)-(+)-carvone (**2**)

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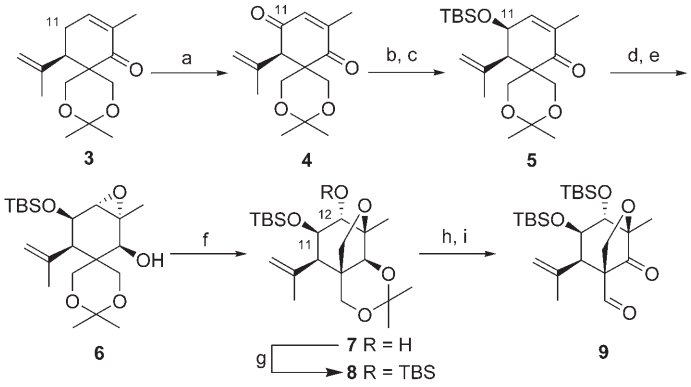
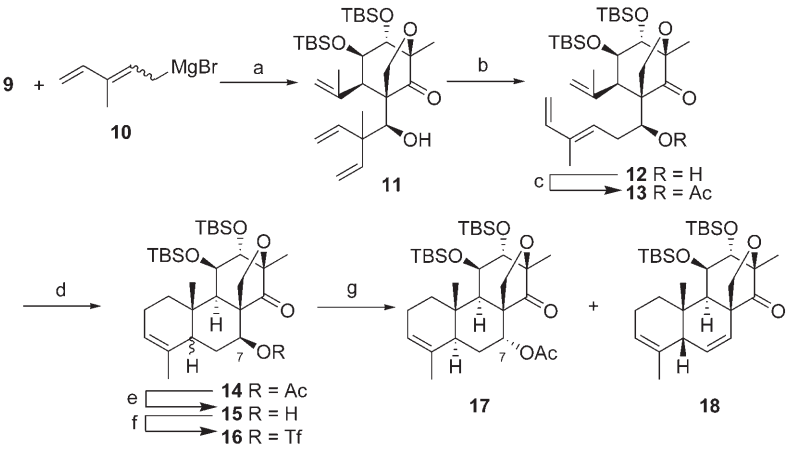
vitro cytotoxicity ($IC_{50} = 0.10\ \mu g\,mL^{-1}$) against KB cells[3] and contains stereogenic centers common to many pentacyclic quassinoids as well as structural requirements and functionalities that are essential for cytotoxicity and solid tumor selectivity.[1] Herein, we report the first short, efficient, and enantiospecific total synthesis of (−)-samaderine Y (**1**) from (*S*)-(+)-carvone (**2**).

On the basis of our previous synthetic endeavors toward pentacyclic quassinoids, we reasoned that the hydroxy group at C11 in ring C of **1** should be secured before the construction of the pentacyclic skeleton.[4] The known enone **3**, which is readily available from (*S*)-(+)-carvone (**2**) in two steps that involve an aldol reaction with formaldehyde and acetonation in an overall yield of 75%,[4] was considered a good starting material for our synthesis (Scheme 1). After extensive experimentation, enone **3** was oxidized regioselectively with CrO_3 and 3,5-dimethylpyrazole[5] at the allylic position at C11 (quassinoid numbering scheme) to give ene-dione **4**. Regio- and stereoselective hydride reduction of the less congested keto group in **4** under Luche conditions[6] from the less hindered α face provided a β-alcohol, which was silylated to give silyl ether **5** in good overall yield. Alkaline hydroperoxide epoxidation of enone **5** at the less hindered α face afforded the α-epoxide, which was subjected to chelation-controlled hydride reduction of the remaining keto group to yield epoxy alcohol **6**. Acid-catalyzed shift of the acetonide diol protecting group accompanied by epoxide-ring opening with an internal hydroxy function in a one-pot procedure furnished ether-bridged **7**. The structure of **7** was confirmed by an X-ray crystallographic study,[7] and the stereocenters in rings C and E were thereby established. Protection of the hydroxy group at C12 in **7** gave disilyl ether **8**. Acid hydrolysis of the acetonide in **8** followed by TPAP-catalyzed[8] oxidation of the resultant 1,3-diol gave rise to keto-aldehyde **9** in 78% overall yield from **7**.

Construction of the AB ring system involved the addition of a six-carbon-atom diene to aldehyde **9** to form the Diels–Alder precursor (Scheme 2). Addition of Grignard reagent **10**[4] to aldehyde **9** generated the 1,4-diene **11** as a single diastereomer (the 1,3-cycloadduct). The stereochemistry of the hydroxy group in **11** was confirmed at a later stage. Fortunately, subsequent [1,3]-sigmatropic rearrangement[9] of 1,4-diene **11** furnished the desired 1,3-diene **12** also as a single diastereomer, in which the alcohol group at C7 was then protected as an acetate to give **13**. The AB ring was constructed by an intramolecular Diels–Alder reaction. Heating triene **13** in toluene at 180 °C afforded *trans*- and *cis*-fused tetracyclic keto-acetate **14** in 2:1 ratio based on ^{1}H NMR spectroscopic studies.[10] Variation of the reaction temperature (140–220 °C), reaction time (48–150 h), and solvent (benzene and benzonitrile) did not affect the ratio of *trans* and *cis* isomers. The two diastereomers could not be separated by column chromatography at this stage but were separated later. Our next aim was to invert the configuration at C7 to the desired α-acetate—the stereochemistry found in natural (−)-samaderine Y (**1**). Base-catalyzed hydrolysis of β-acetate **14** afforded alcohol **15**, which was esterified to give triflate **16**. Nucleophilic substitution of triflate **16** with nBu$_4$NOAc[11] provided α-acetate **17**. No *cis*-fused tetracyclic acetate was obtained. Instead, *cis*-fused tetracyclic 1,4-diene **18** was



Scheme 1. Construction of the CE ring system. Reagents and conditions: a) CrO_3, 3,5-dimethylpyrazole, CH_2Cl_2, reflux, 70% yield (70% conversion); b) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, 0 °C; c) TBSOTf, Et_3N, CH_2Cl_2, room temperature, 87% from **4**; d) TBHP, 2 N NaOH, MeOH, 40 °C; e) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, 0 °C; f) 1. TFA, CH_2Cl_2, room temperature; 2. 2,2-dimethoxypropane, *p*TsOH, room temperature, 73% from **6**; g) TBSOTf, Et_3N, CH_2Cl_2, 100%; h) TFA, H_2O, CH_2Cl_2, room temperature, 92%; i) NMO, TPAP, 3 Å MS, CH_2Cl_2, room temperature, 85%. TBS = *tert*-butyldimethylsilyl; Tf = trifluoromethanesulfonyl; TBHP = *tert*-butylhydroperoxide; TFA = trifluoroacetic acid; Ts = *p*-toluenesulfonyl; NMO = *N*-methylmorpholine *N*-oxide; TPAP = tetrapropylammonium perruthenate; MS = molecular sieves.



Scheme 2. Construction of the AB ring system. a) Et_2O, 0 °C, 78%; b) NaH, 4-methylbenzo[15]crown-5, THF, room temperature; c) Ac_2O, Et_3N, DMAP, CH_2Cl_2, room temperature, 83% from **11**; d) methylene blue, toluene, 180 °C, 92% (2:1 *trans*:*cis*); e) NaOH, MeOH, room temperature; f) Tf_2O, pyridine, DMAP, CH_2Cl_2, room temperature; g) nBu$_4$NOAc, THF, room temperature, **17** (65% from **15**), **18** (31% from **15**). DMAP = 4-(*N*,*N*-dimethylamino)pyridine.

isolated, attributable to hindrance imposed by ring A in which substitution could not proceed smoothly. At this stage, compounds **17** and **18** could be separated by column chromatography.

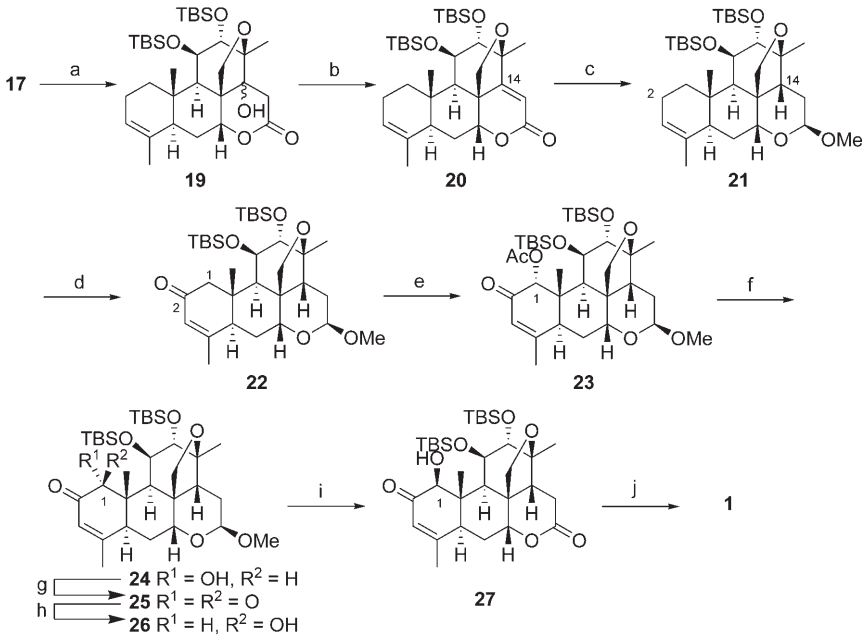
The construction of ring D was our next objective. Intramolecular aldol reaction of acetate **17** gave lactone **19**. The chirality at C14 was introduced in a three-step sequence. Dehydration of the alcohol in **19** afforded α,β-unsaturated lactone **20**. Conjugated reduction[12] of **20** gave rise to the corresponding lactol, which was subjected to acid-catalyzed acetalization with methanol in a one-pot procedure to yield methyl acetal **21** (Scheme 3).

Our remaining task was the functionalization of ring A, and tetracycle **17** was used for model studies (Scheme 4). Oxidation of **17** with classic chromium reagents[13] did not afford enone **28**. After several trials, allylic oxidation of tetracycle **17** did furnish enone **28**.[14] α-Keto acetoxylation[15] of enone **28** gave diacetate **29**, whose structure was confirmed by X-ray crystallography.[7] Following the successful functionalization of ring A of tetracycle **17**, the same procedure was applied to pentacycle **21**.

Allylic oxidation[14] of **21** provided enone **22**, which was subjected to α-keto acetoxylation[15] to give α-acetate **23** as anticipated. The stereogenic center at C1 in **23** had to be inverted before further manipulation could take place. Base hydrolysis of acetate **23** gave alcohol **24**. Acid- or base-catalyzed epimerization of **24** from OH1α to OH1β were unsuccessful. After extensive experimentation, we investigated an oxidation–reduction sequence. Dess–Martin oxidation[16] of alcohol **24** yielded an unstable diketone **25**. Regio- and stereoselective hydride reduction of the carbonyl at C1 in diketone **25** afforded β-alcohol **26**. Acid hydrolysis of acetal **26** gave rise to the corresponding lactol, which was oxidized with Ag_2CO_3 on celite[17] to yield lactone **27**.

Our last objective was the removal of the two silyl ethers, however, conventional desilylation conditions were unsuccessful. After extensive experimentation, the use of concentrated HCl with TFA as the solvent at room temperature led to the smooth removal of the silyl ether groups and gave the target molecule (−)-samaderine Y (**1**) in 61% yield. The physical and spectral data of synthetic **1** were in full accordance with those reported in the literature in all respects.[3]

In summary, (−)-samaderine Y (**1**) was constructed in 21 steps from (*S*)-(+)-carvone (**2**), with an average yield of 81% for each step. This relatively short synthesis opens feasible avenues for the preparation of other optically active pentacyclic quassinoids and analogues for biological evaluation. Research aimed in this direction is in progress.



Scheme 3. Synthesis of (−)-samaderine Y (**1**). a) LDA, THF, −78 °C, 88%; b) $SOCl_2$, pyridine, CH_2Cl_2, 45 °C, 94%; c) 1. $NaBH_4$, $NiCl_2 \cdot 6H_2O$, MeOH, room temperature; 2. conc. HCl, room temperature, 78%; d) 10 mol% $Mn(OAc)_3 \cdot 2H_2O$, TBHP, 3 Å MS, EtOAc, room temperature, 72%; e) $Mn(OAc)_3 \cdot 2H_2O$, benzene, reflux, 78%; f) K_2CO_3, MeOH, room temperature, 90%; g) Dess–Martin periodinane, CH_2Cl_2, room temperature; h) $NaBH_4$, THF, MeOH, 0 °C, 80% from **24**; i) 1. conc. HCl, H_2O, THF, 45 °C; 2. Ag_2CO_3/celite, benzene, reflux, 68%; j) conc. HCl, TFA, room temperature, 61%. LDA = lithium diisopropylamide.

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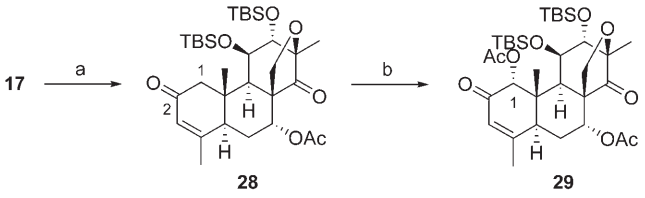

Scheme 4. Functionalization of ring A. a) 10 mol% $Mn(OAc)_3 \cdot 2H_2O$, TBHP, 3 Å MS, EtOAc, room temperature, 70%; b) $Mn(OAc)_3 \cdot 2H_2O$, benzene, reflux, 78%.

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