DOI: 10.1002/chem.200600669

Synthetic Studies towards Pentacyclic Quassinoids: Total Synthesis of Unnatural (−)-14-*epi*-Samaderine E and Natural (−)-Samaderine Y from (*S*)-(+)-Carvone**

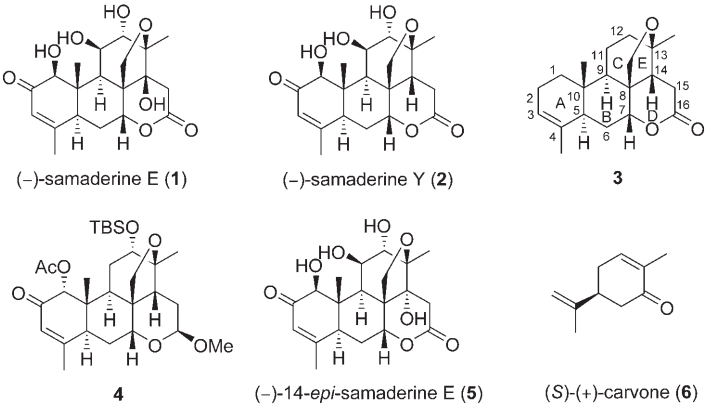
Tony K. M. Shing* and Ying-Yeung Yeung[a]

Abstract: First total syntheses of unnatural (−)-14-*epi*-samaderine E (**5**) and natural (−)-samaderine Y (**2**) were accomplished from (*S*)-(+)-carvone (**6**) in 18 and 21 steps, respectively. The syntheses are short, efficient (with an average yield of 80% plus for each transformation), enantiospecific, and produce nine new chiral centers. The crucial points of the syntheses included a regioselective allylic oxidation on ring C, regio- and stereoselective reduction of ketone, a stereocontrolled epoxidation, an epoxymethano-bridge formation, a chemoselective Grignard reaction, an intramolecular Diels–Alder reaction, an intramolecular aldol addition, and a newly developed manganese(III)-catalyzed allylic oxidation on ring A.

Keywords: allylic oxidation · antitumor agents · cycloaddition · quassinoids · total synthesis

Introduction

(−)-Samaderine E (**1**) and (−)-samaderine Y (**2**) are pentacyclic quassinoids[1] isolated from *Quassia indica* and characterized in 1977[1a] and 1994,[1e] respectively. (−)-Samaderine Y (**2**) was shown to exhibit in vitro cytotoxicity (IC_{50} = 0.10 μg mL^{-1}) against KB cells.[1f] For (−)-samaderine E (**1**), both in vitro cytotoxicity (KB cells IC_{50} = 0.04 μg mL^{-1}) and nematocidal activity (MCL = 2.0×10^{-5} M) were documented.[1e,f] Their structures are very similar except for the oxidation level at the C14 position.[2] They share the same skeleton **3** and possess ten stereogenic centers that are common to many pentacyclic quassinoids.[1a] The structural features and functionalities present in **1** and **2** are essential for cytotoxicity and solid tumor selectivity.[2]



Total synthesis of quassimarin [3a] simalikalactone D,[3b] pentacyclic quassinoids related to (−)-samaderine Y (**2**), was accomplished by Grieco and co-workers, but the route was lengthy and inefficient. For (−)-samaderine E (**1**), neither synthetic study nor total synthesis was reported, probably caused by the difficulty in the installation of the highly hindered C14 hydroxyl functionality.

In our previous studies, we have already demonstrated the synthesis of an advanced pentacyclic quassinoid intermediate **4** by using (*S*)-(+)-carvone (**6**) as the starting material.[4] However, problems were encountered during the introduction of a hydroxyl group at C11 of **4**, presumably due to the sensitive enone moiety. We therefore explored an alternative synthetic pathway towards pentacyclic quassinoids by a complete functionalization of the ring C at an early stage.

[a] Prof. Dr. T. K. M. Shing, Y.-Y. Yeung
Department of Chemistry and Center of Novel Functional Molecules
The Chinese University of Hong Kong
Shatin, NT, Hong Kong(China)
Fax: (+852) 2-6035-057
E-mail: tonyshing@cuhk.edu.hk

[**] Part of this work was published as a preliminary communication: T. K. M. Shing, Y. Y. Yeung, *Angew. Chem.* **2005**, *117*, 8195–8198; *Angew. Chem. Int. Ed. Engl.* **2005**, 44, 7981–7984.

Supporting information for this article is available on the WWW under http://www.chemeurj.org/ or from the author.

The present paper describes our synthetic effort towards the first, efficient construction of unnatural (−)-14-*epi*-samaderine E (**5**) and natural (−)-samaderine Y (**2**), involving stereoselective hydride reductions, epoxidation, Grignard addition, intramolecular Diels–Alder reaction, allylic oxidation, and intramolecular aldol addition as the salient reactions. A preliminary account on the synthesis of natural (−)-samaderine Y (**2**) has already been published.[5]

Results and Discussion

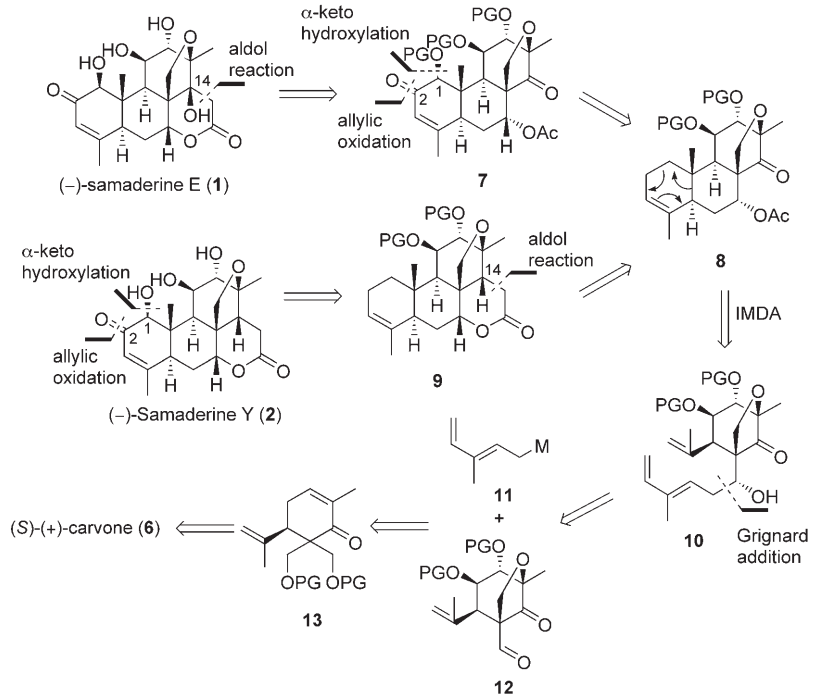
Retrosynthetic analysis: Our synthetic plans towards (−)-samaderine E (**1**) and (−)-samaderine Y (**2**) were based on a C→CE→ABCE→ABCDE ring annulation sequence.[6] For (−)-samaderine E (**1**), the lactone (D ring) could be constructed by an intramolecular aldol addition reaction of ester **7** (Scheme 1). The oxygen functionalities in ring A of **7** could be derived from tetracyclic ketone **8** through α-hydroxylation and allylic oxidation. In a similar manner, (−)-samaderine Y (**2**) could be derived from pentacyclic lactone **9** by sequential oxidation of ring A. We reasoned that the D ring in **2** should be installed first before functionalization of ring A, but the lactone carbonyl group had to be masked as it could not survive the oxidation conditions during the functionalization of ring A, as indicated in our previous research.[6c] The lactone (D ring) in **9** could be assembled by means of an intramolecular aldol reaction from the same synthetic intermediate **8** as that in the synthesis of (−)-samaderine E (**1**).

The AB ring in tetracycle **8** could be fabricated from triene **10** by an intramolecular Diels–Alder (IMDA) reaction. The 1,3-diene moiety could be installed by nucleophilic addition of an organometallic olefin **11** to the corresponding aldehyde **12**. The functionalization of ring C and the formation of ring E could be accomplished by sequential oxidation of enone **13** which could be transformed from (*S*)-(+)-carvone (**6**).

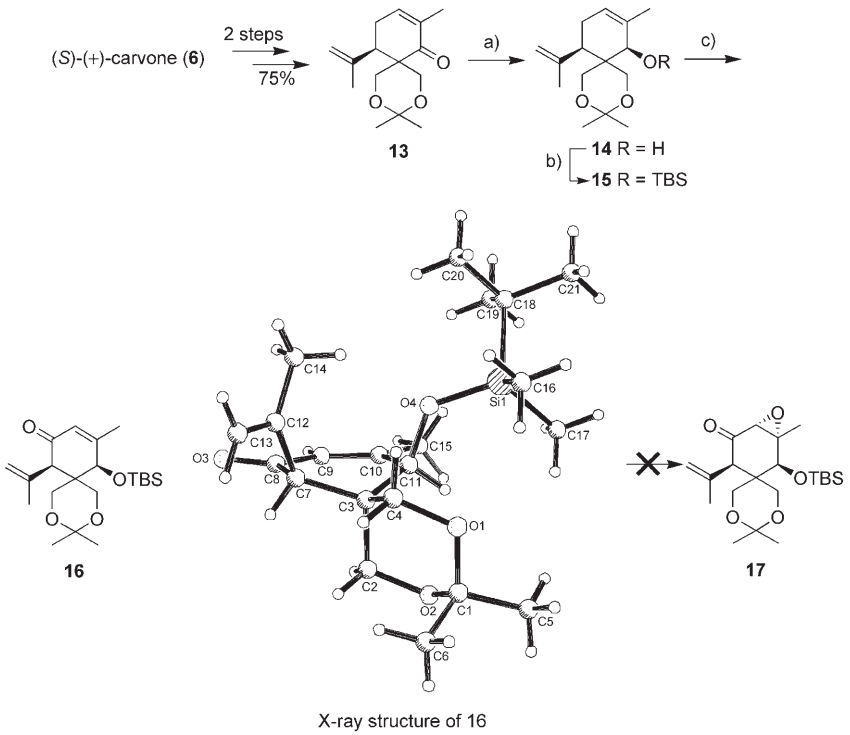
Synthesis of the fully functionalized CE ring: We reasoned that regioselective allylic oxidation of the methylene group should be a suitable reaction to functionalize C11 of enone **13**, which was readily prepared in two steps from (*S*)-(+)-carvone (**6**), a good starting material for our synthesis.[4] $NaBH_4$ reduction of enone **13** under Luche conditions[7] gave allyl alcohol **14** in which the hydride attacked the carbonyl group from the less hindered α-face (Scheme 2). Protection of β-alcohol **14** with TBSOTf afforded silyl ether **15**. Allylic oxidation of **15** with chromium trioxide and 3,5-dimethylpyrazole[8] in dichloromethane furnished enone **16** (80% yield from **13**) in which C11 was successfully functionalized. The structure of **16** was confirmed by an X-ray crystallographic study.[9] We attempted to introduce C12,13 oxygen functionalities by epoxidation; however, treatment of enone **16** with $tBuO_2H$ and various bases including NaOH, K_2CO_3, or Triton B did not give the desired epoxide **17**.[10]

We then attempted to construct the E ring. Unmasking the silyl ether **16** with TBAF in THF gave allyl alcohol **18** (Scheme 3). TFA-catalyzed intramolecular Michael reaction[11] accompanied by an acetonide shift afforded ketone **19**. The structure of ketone **19** was confirmed by an X-ray crystallographic study.[9] We speculated that the C12 hydroxyl group could be established by an α-keto hydroxylation (**19**→**20**). However, treating ketone **19** with LDA in THF at −78 °C produced a complex mixture, probably suffering from epimerization and isomerization of the *iso*-propenyl moiety.

After extensive experimentation, enone **13** was oxidized at the C11 allylic position regioselectively by chromium trioxide and 3,5-dimethylpyrazole[8] in CH_2Cl_2 at refluxing temperature to give ene-dione **21** in 70% yield, based on 70% conversion (Scheme 4). Classically, oxidation of enone to ene-dione usually involved harsh oxidation conditions or the recent palladium[12] or rhodium-based[13] catalysts. The feasibility of the conversion of enone **13** into ene-dione **21** was probably attributable to activation of the allylic C11 by the electron donating β-methyl group.



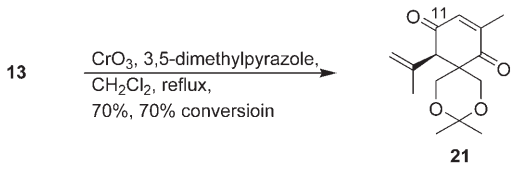
Scheme 1. Retrosynthetic analysis. PG = protecting group.



Scheme 2. Attempted synthesis of enone **17**. a) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, 0°C; b) TBSOTf, Et_3N, CH_2Cl_2, RT; c) CrO_3, 3,5-dimethylpyrazole, CH_2Cl_2, RT, 80% from **13**. TBSOTf = *tert*-Butyldimethylsilyl trifluoromethanesulfonate, TBS = *tert*-butyldimethylsilyl.

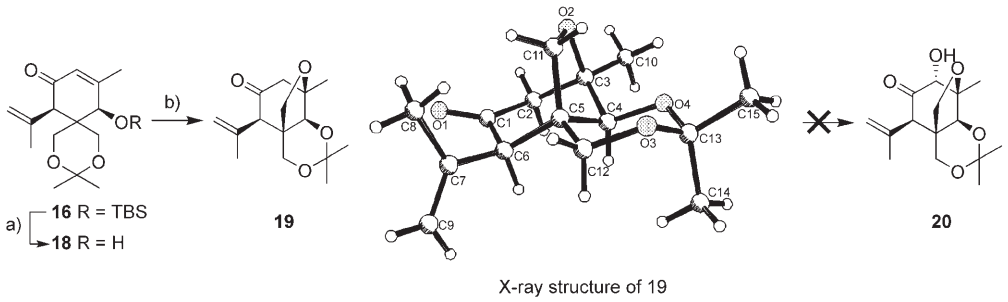
As we had functionalized C11, our next mission was to construct the E ring. In a model study, epoxymethano bridge formation to give **24** from epoxide **22** had been demonstrated previously by a stepwise acid-promoted transformation (Scheme 5).[14] Subsequently, the reaction was improved in yields, under acid-catalyzed conditions, which were similar to those for the transformation of **18** to **19**, at room temperature, and in one pot. Hence, the conversion (**22**→**24**) was completed within 30 minutes in 91% overall yield. On the basis of this synthetic strategy, we anticipated to construct a fully functionalized CE ring from **21**.

As the α-isopropenyl ketone moiety in ring C was unstable, the C11 keto group in **21** was reduced before the formation of ring E. Reduction of ene-dione **21** under Luche conditions,[7] in which the hydride anion regioselectively attacked the less hindered C11 carbonyl group stereoselectively from the less hindered α-face, gave β-alcohol **25** (Scheme 6). Subsequent protection of alcohol **25** with TBSOTf furnished silyl ether **26**. With the correct alcohol stereochemistry at the C11 position established, we proceeded with the synthesis according to our ring E construction strategy. Stereoselective epoxidation of the double bond in enone **26** at the less hindered α-face with alkaline $tBuO_2H$ afforded α-epoxide **27**. Chelation-controlled reduction of ketone **27** with $NaBH_4$ and $CeCl_3{\cdot}7H_2O$[7] in which the hydride attacked from the α-face, gave alcohol **28**. Acid-catalyzed shift of the acetonide-protecting group accompanied by epoxide ring opening with an internal hydroxyl function in a one-pot procedure furnished tricyclic alcohol **29** in 73% overall yield from enone **26**. The structure of tricyclic alcohol **29** was confirmed by an X-ray crystallographic study.[9] Protection of the C12 hydroxyl group in **29** with TBSOTf afforded disilyl ether **30** in a quantitative yield. At this stage, we had already constructed the CE ring skeleton with correct functionalities and chiralities.

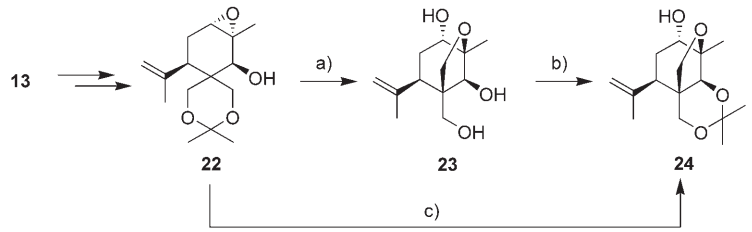


Scheme 4. Synthesis of ene-dione **21**.

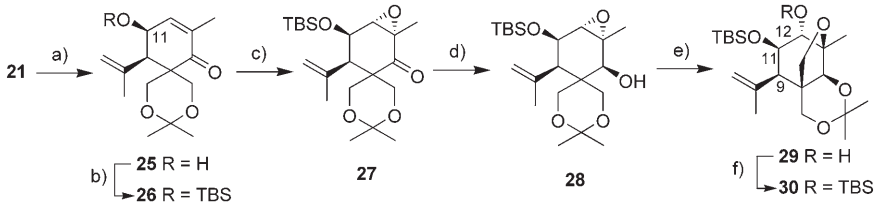
Synthesis of ABCE ring skeleton: Our next mission was to construct the AB ring. Acid hydrolysis of tricycle **30** with



Scheme 3. Attempted synthesis of **20**. a) TBAF, THF, RT; b) 1) TFA, CH_2Cl_2, RT, 2) *p*TsOH, 2,2-dimethoxypropane, RT, 95% from **16**. TBAF = tetrabutylammonium fluoride; TFA = trifluoroacetic acid; Ts = tosyl.

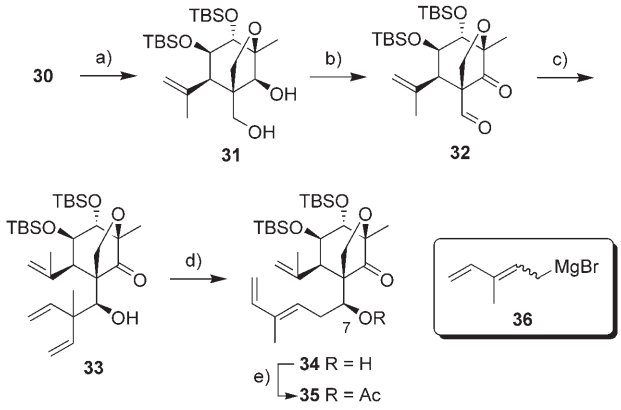


Scheme 5. Synthesis of **24**. a) TFA, EtOH, 50 °C; b) 2,2-dimethoxypropane, *p*TsOH, CH_2Cl_2, RT, 40 %; c) 1) TFA, CH_2Cl_2, RT, 2) 2,2-dimethoxypropane, *p*TsOH, RT, overall 91 %.



Scheme 6. Synthesis of **30**. a) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, 0 °C; b) TBSOTf, Et_3N, CH_2Cl_2, 0 °C to RT, 87 % from **21**; c) *t*BuO_2H, NaOH, MeOH, 45 °C; d) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, 0 °C; e) 1) TFA, CH_2Cl_2, RT, 2) *p*TsOH, 2,2-dimethoxypropane, RT, 73 % from **26**; f) TBSOTf, Et_3N, CH_2Cl_2, 0 °C to RT, 100 %.

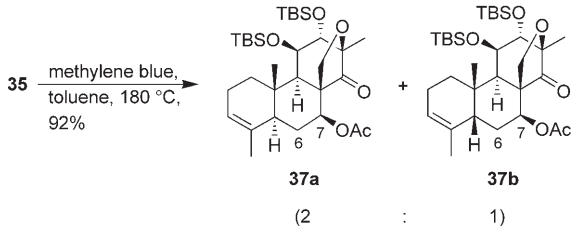
aqueous TFA gave 1,3-diol **31** in 92 % yield (Scheme 7). TPAP-catalyzed[15] oxidation of 1,3-diol **31** gave rise to keto-



Scheme 7. Synthesis of IMDA precursor **35**. a) TFA, H_2O, CH_2Cl_2, RT, 92 %; b) cat. TPAP, NMO, 3 Å MS, CH_2Cl_2, RT, 85 %; c) Grignard reagent **36**, Et_2O, 0 °C, 78 %; d) NaH, 4-methylbenzo-15-crown-5, THF, RT; e) Ac_2O, Et_3N. DMAP, CH_2Cl_2, RT, 83 % from **33**. TPAP = tetra-*n*-propylammonium perruthenate; NMO = *N*-methylmorpholine-*N*-oxide; DMAP = 4-dimethylaminopyridine.

aldehyde **32** in 85 % yield. Chemoselective addition of Grignard reagent **36**,[4] which was readily prepared from ethyl acetate, to aldehyde **32** gave 1,4-diene **33** in 78 % yield. This result was consistent with our previous studies,[4] presumably ascribable to the rigidity of the CE ring system. The stereochemistry of the hydroxy group in **33** could not be assigned at this stage but was confirmed later. [1,3]-Sigmatropic rearrangement[16] of 1,4-diene **33** to the desired 1,3-diene **34** was induced by treatment with NaH in the presence of 4-methylbenzo-15-crown-5 at room temperature, providing **34** as a single diastereomer (C7β, confirmed after the construction of the AB ring). Alcohol **34** was protected as the acetate by reaction with Ac_2O to give **35** in 83 % yield from **33**. With the IMDA precursor **35** in hand, our next mission was the construction of the AB ring.

Heating triene **35** in toluene with a catalytic amount of methylene blue[17] at 180 °C afforded the desired *trans*-fused tetracyclic keto-acetate **37a** (Scheme 8). However, a structural isomer, tentatively assigned as *cis*-fused tetracyclic keto-acetate **37b**, was also obtained from the reaction. The ratio of **37a** to **37b** was shown

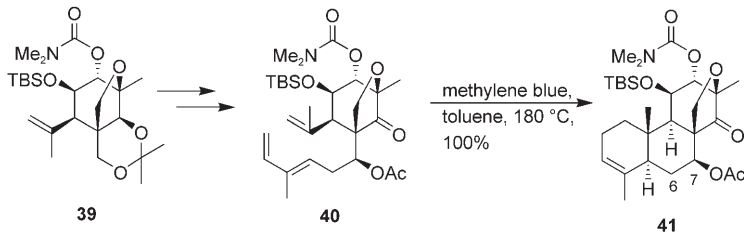


Scheme 8. Intramolecular Diels–Alder reaction of **35**.

to be 2:1 by ^{1}H NMR spectroscopic studies (**37a**: δ = 5.73 ppm, doublet of doublets, J(H7,H6α) = 5.4, 12.0 Hz; **37b**: δ = 5.48 ppm, doublet of doublets, J(H7,H6α) = 4.5, 12.3 Hz). The large coupling constants between H-6 and H-7 indicated the OAc7β stereochemistry in both **37a** and **37b**.

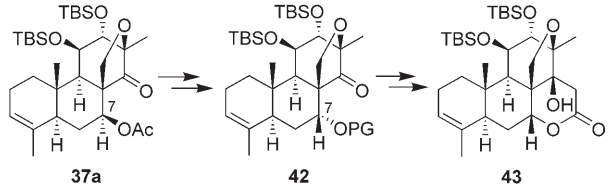
On the other hand, triene **40**, which had readily been prepared from **39**[14] under similar conditions,[4] as in the transformation of **30** into **35**, underwent IMDA cyclization at 180 °C (Scheme 9) to furnish *trans*-fused tetracycle **41** as a single diastereomer in a quantitative yield. We propose that the bulky disilyl ether in **35** distorts the C ring in such a way that the difference between the thermodynamic stability of **37a** and **37b** becomes smaller.

It was unfortunate that the *trans*- to *cis*-isomer ratio (**37a**/**37b** 2:1) was quite close, although the desired *trans* isomer **37a** was the major product. Another problem was that the two isomers, **37a** and **37b**, could not be separated by flash-column chromatography. Endeavors involving changes in reaction temperature (140–220 °C), time (48–150 h), and solvent (benzene and benzonitrile) could not alter the ratio of the *trans* to *cis* isomer.[18] Under this circumstance, we proceeded with the synthesis to see whether the two isomers



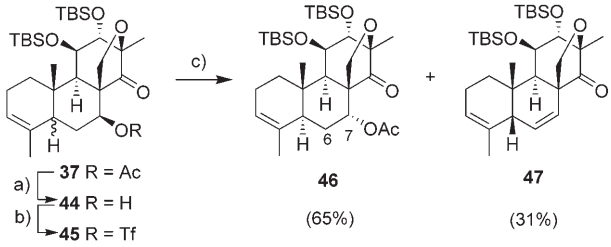
Scheme 9. IMDA reaction of triene **40**.

would be chromatographically separable at a later stage. Our next mission was to invert the chiral center at C7 from β-face (**37a**) to α-face (**42**)—the stereochemistry found in natural pentacyclic quassinoids. The ester **42** would be a precursor for an aldol cyclization to give lactone **43** (Scheme 10).



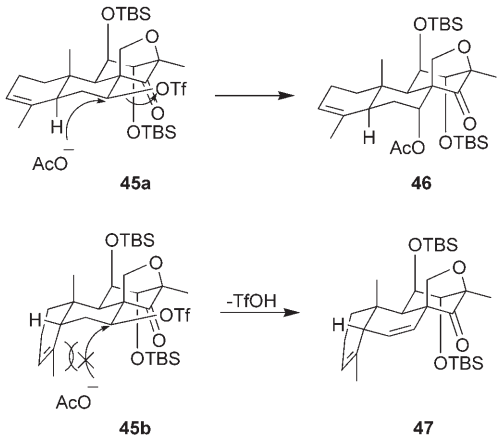
Scheme 10. Approach towards formation of the D Ring.

Base hydrolysis of β-acetates **37a** and **37b** with sodium hydroxide in methanol provided chromatographically inseparable alcohols **44a** and **44b** in 95% yield (Scheme 11). Attempts to epimerize C7 by an oxidation–reduction sequence[4] were unsuccessful. We then turned to a displacement strategy. Esterification of alcohols **44a** and **44b** with Tf_2O gave triflates **45a** and **45b**. Substitution of triflates **45a** and **45b** with nucleophilic acetate (tetra-*n*-butylammonium acetate)[19] in THF at room temperature afforded *trans*-fused tetracyclic acetate **46** in 65% overall yield from **44**. The small coupling constant between H6 and H7 ($\delta = 5.42$ ppm, triplet, $J(H7,H6) = 2.7$ Hz) was consistent with the structure of OAc7α **46**. In the same reaction, no *cis*-fused tetracyclic acetate was obtained. Instead, *cis*-fused tetracyclic 1,4-diene **47** was isolated in 31% yield.



Scheme 11. Synthesis of **46**. a) NaOH, MeOH, RT, 95%; b) Tf_2O, pyridine, DMAP, CH_2Cl_2, RT; c) nBu_4NOAc, THF, RT, **46** (65% from **44**), **47** (31% from **44**).

We rationalize that for the *cis*-fused tetracycle **45b**, the α-face was hindered by ring A in which nucleophilic substitution could not proceed smoothly and elimination of triflic acid was the preferred pathway (Scheme 12). At this stage, *trans*-fused tetracyclic acetate **46** and *cis*-fused tetracyclic diene **47** were separated by flash-column chromatography, but the drawback was the loss of a substantial amount of the desired synthetic intermediate **46**.

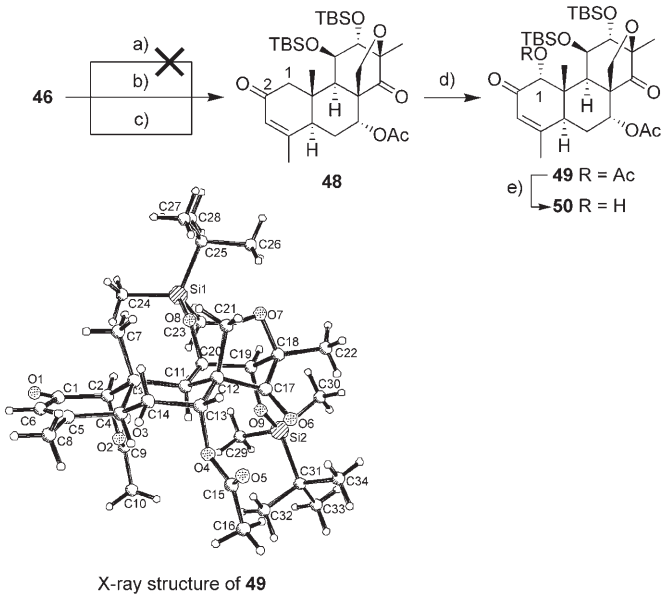


Scheme 12. Proposed mechanism for the nucleophilic displacement of **45**.

Total synthesis of unnatural (−)-14-*epi*-samaderine E: With tetracycle **46** in hand, we anticipated to make (−)-samaderine E (**1**) by functionalization of the A ring through an allylic oxidation as the first step. After several attempts including the use of chromium trioxide/3,5-dimethylpyazole,[8] chromium hexacarbonyl/$tBuO_2H$,[20] and manganese(III) acetate dihydrate/*tert*-butylhydroperoxide,[21] manganese(III)-catalyzed allylic oxidation[21] of tetracycle **46** gave the best yield of enone **48** (Scheme 13).

α-Keto acetoxylation[22] of enone **48** with manganese(III) acetate dihydrate in benzene at refluxing temperature proceeded with a Dean–Stark apparatus to give α-acetate **49** in 78% yield. The structure of acetate **49** was confirmed by an X-ray crystallographic study.[9]

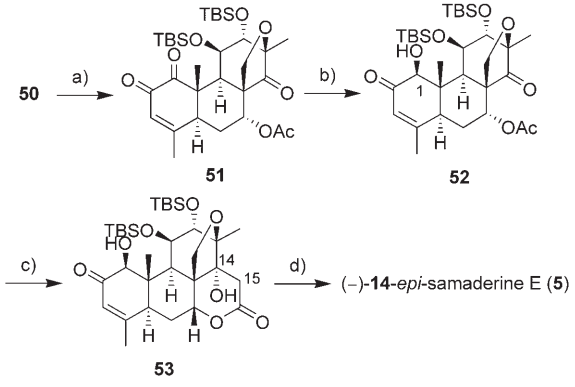
Our next mission was to invert the chiral center at C1 in **49**. Selective saponification of the C1 acetate in **49** with potassium carbonate in methanol at room temperature gave the corresponding alcohol **50** in 96% yield. Acid- (TFA or *p*-toluenesulfonic acid) or base-catalyzed (K_2CO_3/MeOH, NaOH/MeOH, NaH/THF, DBU/CH_2Cl_2, or MeOH) epimerization from OH1α **50** to OH1β **52** were all fruitless. Activation of alcohol (Tf_2O) followed by nucleophilic substitution with wet DMF[23] or inversion of alcohol with DCCI (DCCI = dicyclohexyl carbodiimide)[24] or Mitsunobu reac-



Scheme 13. Synthesis of **50**. a) CrO_3, 3,5-dimethylpyrazole, CH_2Cl_2, RT; b) $Cr(CO)_6$, tBuO$_2$H, MeCN, reflux, 60%; c) 10 mol% $Mn(OAc)_3 \cdot 2H_2O$, tBuO$_2$H, 3 Å MS, EtOAc, RT, 70%; d) $Mn(OAc)_3 \cdot 2H_2O$, benzene, reflux, 78%; e) K_2CO_3, MeOH, RT, 96%.

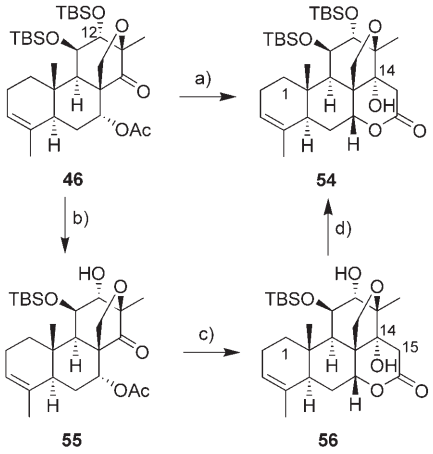
tion[25] did not give the desired product, beyond decomposition of the starting material. These negative results were consistent with those reported by Grieco in which a cholesterol derivative was used as a model study for the similar transformation.[26]

We then attempted to epimerize OH1 in **50** with an oxidation–reduction sequence. Oxidation in a basic media was not suitable as tetracycle **50** was basic sensitive, ascribable to the presence of the enone moiety. Instead, mildly acidic Dess–Martin reagent[27] was successfully applied to alcohol **50** to give a highly unstable tri-ketone **51** (Scheme 14). Carefully controlled $NaBH_4$ reduction of tri-ketone **51** in THF and methanol (9:1 v/v) at 0°C proceeded, with the hydride anion attacking regioselectively at the most reactive and the least hindered C1 ketone and stereoselectively from the less hindered α-face, to give β-alcohol **52**.



Scheme 14. Synthesis of **5**. a) Dess–Martin periodinane, CH_2Cl_2, RT; b) $NaBH_4$, THF/MeOH 9:1, v/v, 0°C, 85% from **50**; c) LDA, THF, −78°C, 80%; d) TFA, H_2O, RT, 71%. LDA = lithium diisopropylamide.

Protection of the free hydroxyl group in **52** with TBSOTf or ethoxymethyl chloride was unsuccessful. Fortunately, direct LDA-promoted intramolecular aldol reaction of keto-acetate **52** at −78°C furnished 14α-hydroxy lactone **53** in 80% yield. This result was quite unusual, as the enolate-derived from OAc7α should attack from the α-face, resulting in the formation of the anticipated OH14β aldol adduct.[6c] Intramolecular aldol reaction of tetracycle **46** under the same conditions also gave the same kind of OH14α lactone adduct **54** (Scheme 15). The structure of pentacyclic lactone



Scheme 15. Aldol reaction of **46**. a) LDA, THF, −78°C, 88%; b) TBAF, THF, 0°C; c) LDA, THF, −78°C; TBSOTf, Et_3N, CH_2Cl_2, RT, 62% from **46**.

54 was confirmed by an X-ray crystallographic study (Figure 1).[9] The structure shows a highly distorted BCD ring, with OH14 at the α-face.

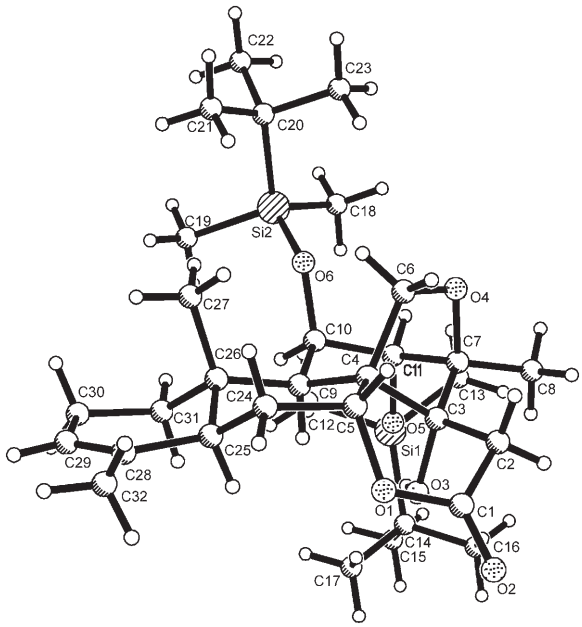


Figure 1. X-ray structure of pentacyclic lactone **54**.

Changing the solvent (toluene, diethyl ether), base (NaHMDS; HMDS = hexamethyldisilazane), enolization method (BCl_3, pyridine),[28] or reaction temperature (−78, −30, 0 °C, RT) of the intramolecular aldol reaction did not give any desired OH14β aldol product. We suspected that the C12-*tert*-butyldimethylsiloxy group in **46** might obstruct the α-attack of the ketone. Carefully controlled regioselective desilylation of the C12-silyl group in **46** with TBAF at 0 °C afforded alcohol **55**. Treatment of **55** with LDA at −78 °C gave pentacyclic lactone **56**. However, upon silylation of **56** with TBSOTf, disilyl ether **54** was obtained, identical to the aldol adduct derived directly from **46** (Scheme 15).

The ^{1}H NMR spectra of hydroxy-lactones **53** and **54** show that their H15 resonances are consistent with the lactone moiety (Figure 2) and display a characteristic doublet of doublets at $\delta = \sim 2.8$ ppm. The H7 of keto-acetate **52** shows small coupling constants with H6 ($\delta = 5.47$ ppm, doublet of doublets, J(H7,H6α) = 2.1, 3.6 Hz). After intramolecular aldol cyclization, only one larger coupling constant between H7 and H6 in hydroxy-lactone **53** is observed, accompanied by an upfield shift of H7 ($\delta = 4.45$ ppm, doublet, J(H7,H6) = 4.8 Hz), which indicated the formation of a distorted BD ring. Similar ^{1}H NMR spectroscopic patterns for H7 of keto-acetate **46** ($\delta = 5.42$ ppm, triplet, J(H7,H6) = 2.7 Hz) and of hydroxy-lactone **54** ($\delta = 4.44$ ppm, doublet, J(H7,H6) = 5.7 Hz) are also observed (Figure 2). A rationalization for the stereochemical outcome of the intramolecular aldol reaction (**52**→**53** and **46**→**54**) was that the epoxymethano bridge held the C ring rigidly and the ketone moiety was flipped downward, hence the enolate anion of **52** or **46** could only attack from the β-face.

With the C14 epimer **53** in hand, deprotection would complete the synthesis of 14-*epi*-samaderine E (**5**). Treatment of disilyl ether **53** with TBAF gave a complex mixture. Other fluoride reagents including TBAF/acetic acid,[29] NH_4HF/DMF,[30] or TBAF/2BF_3[31] did not afford the desired target. As lactone **53** is base sensitive due to the presence of the enone moiety, acidic reagent should be suitable to remove the silyl ethers. Reagents including concentrated HCl/H_2O,[32] BF_3/CH_2Cl_2,[33] or HF/CH_3CN[34] were used, but the deprotection was unsuccessful. After extensive studies, desilylation proceeded smoothly in aqueous TFA,[35] giving (−)-14-*epi*-samaderine E (**5**) in 71 % yield

Total synthesis of natural (−)-samaderine Y: For our next mission towards the total synthesis of (−)-samaderine Y (**2**), ring D should be constructed first before functionalization of ring A, but the lactone carbonyl group had to be masked as it could not survive the oxidation conditions during the functionalization of ring A according to our experience.[6c] Thionyl chloride-mediated dehydration[36] of alcohol **54** afforded α,β-unsaturated lactone **57** in 94 % yield (Scheme 16). The structure of **57** was confirmed by an X-ray crystallographic study (Figure 3).[9] Nickel boride-mediated ($NiCl_2 \cdot 6H_2O$ and sodium borohydride)[4,6,37] conjugate reduction of α,β-unsaturated lactone **57**, in which the hydride attacked from the less hindered β-face, gave the corresponding lactol which was then protected in the form of an acetal by acid-catalyzed acetalization, providing acetal **58** in 78 %

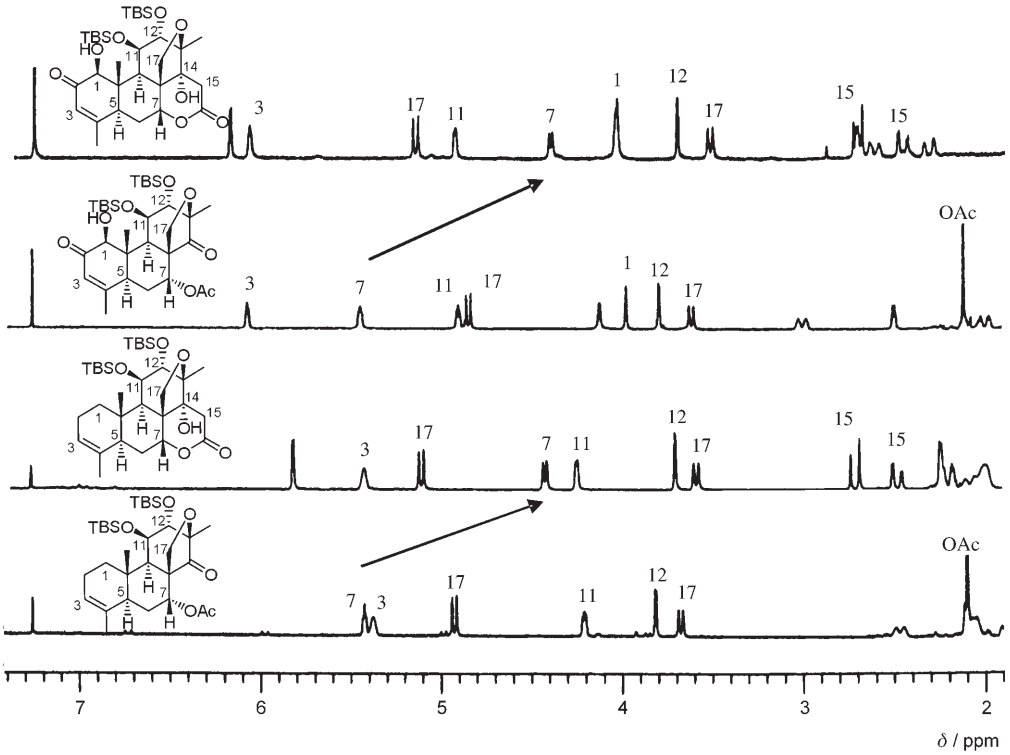
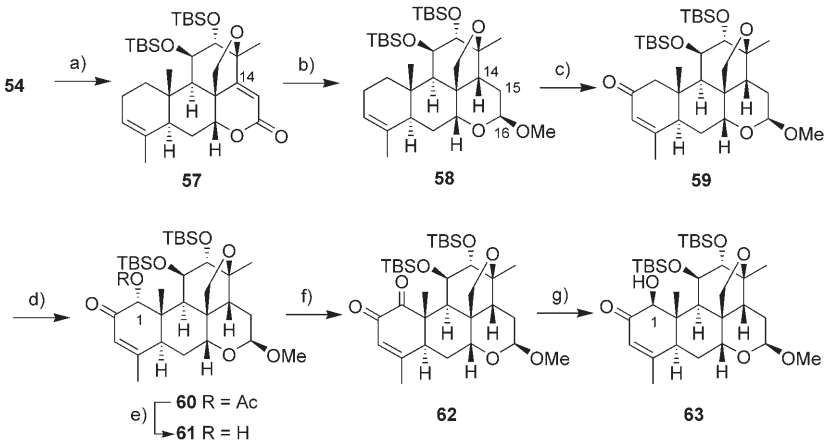


Figure 2. Comparison of the ^{1}H NMR spectra of **53**, **52**, **54**, and **46**.



Scheme 16. Synthesis of **63**. a) $SOCl_2$, pyridine, CH_2Cl_2, 45 °C, 94 %; b) 1) $NaBH_4$, $NiCl_2{\cdot}6H_2O$, MeOH, 0 °C to RT, 2) concd HCl, RT, 78 %; c) 10 mol % $Mn(OAc)_3{\cdot}2H_2O$, $tBuO_2H$, 3 Å MS, EtOAc, RT, 72 %; d) $Mn(OAc)_3{\cdot}2H_2O$, benzene, reflux, 78 %; e) K_2CO_3, MeOH, RT, 90 %; f) Dess–Martin periodinane, CH_2Cl_2, RT; g) $NaBH_4$, THF/MeOH 9:1, v/v, 0 °C, 80 % from **61**.

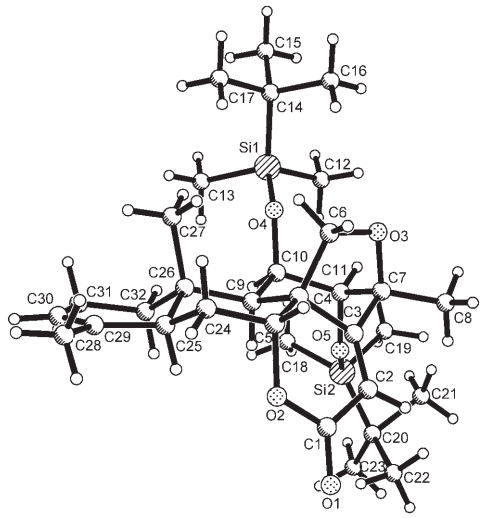


Figure 3. X-ray structure of **57**.

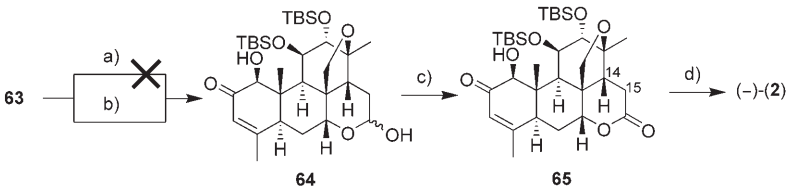
yield. A small H16,15 coupling constant ($\delta = 4.77$ ppm, doublet, J(H16,H15) = 3.0 Hz) indicated the C16β-methoxy stereochemistry in **58**. With pentacycle **58** in hand, we proceeded to functionalize ring A under conditions similar to those in the synthesis of (−)-14-*epi*-samaderine E (**5**).

Manganese(III) acetate-catalyzed allylic oxidation[21] of cyclohexene **58** with $tBuO_2H$ as co-oxidant in EtOAc at RT afforded enone **59** in 72 % yield. Boiling enone **59** with $Mn(OAc)_3{\cdot}2H_2O$ in benzene[22] by using a Dean–Stark apparatus to separate the water of crystallization gave acetate **60** in 78 % yield. Base hydrolysis of acetate **60** with K_2CO_3 in methanol furnished alcohol **61** in 74 % yield. Dess–Martin oxidation[27] of alcohol **61** at room temperature gave an unstable diketone **62**. Regio- and stereoselective reduction of diketone **62** with $NaBH_4$ in THF and methanol as co-solvents at 0 °C furnished C1β alcohol **63** in 80 % yield from **61**. At this stage, our remaining task was the unmasking of the protecting groups.

When pentacycle **63** was heated in aqueous acetic acid at reflux, however, a complex mixture was obtained (Scheme 17). Changing the conditions to heating pentacycle **63** in aqueous THF with concentrated HCl at 45 °C gave the corresponding lactol **64**. Oxidation of lactol **64** with Fetizon's reagent[38] in benzene at reflux provided lactone **65** in 68 % overall yield from **63**. Our last mission was the removal of the two silyl ethers. On the basis of our experience with disilyl ether **53**, we therefore attempted to unmask **65** with aqueous TFA. However, no positive result was obtained. Heating **65** in aqueous HCl could only give a trace amount of product, with decomposition of the starting material as the major pathway. After extensive studies, the use of concentrated HCl with TFA as the solvent at room temperature led to smooth removal of the silyl ethers, giving the target molecule (−)-samaderine Y (**2**) in 61 % yield. The physical and spectral data of synthetic (−)-samaderine Y (**2**) were in full accordance with the literature values[1e,f] in all respects.

Conclusion

Unnatural (−)-14-*epi*-samaderine E (**5**) and natural (−)-samaderine Y (**2**) were synthesized from (*S*)-(+)-carvone (**6**) in 18 and 21 steps, respectively. The efficient (with an average yield of 80 % plus for each transformation), relatively short first construction of pentacyclic quassinoid analogue (−)-14-*epi*-samaderine E (**1**) with a C14 hydroxy functionality and the first total synthesis of (−)-samaderine Y (**2**) open feasible avenues for the preparation of other optically active pentacyclic quassinoids and analogues for biological evaluation. Research in this direction is in progress.



Scheme 17. Synthesis of (−)-samaderine Y (**2**). a) AcOH, H_2O, reflux; b) concd HCl, H_2O, THF, 45 °C; c) Ag_2CO_3, Celite, benzene, reflux, 68 % from **63**; d) concd HCl, TFA, RT, 61 %.

Experimental Section

General: Experimental procedures already appeared in the Supporting Information of the preliminary account[5] on the synthesis of natural (−)-samaderine Y (**2**) and are not repeated here. Melting points were measured with a Reichert apparatus in degrees Celsius and are uncorrected. Optical rotations were obtained with a Perkin–Elmer model 341 polarimeter, operating at 589 nm. IR spectra were recorded on a Nicolet 205 or a Perkin–Elmer 1600 FTIR spectrophotometer as thin films on potassium bromide discs. NMR spectra were measured with a Bruker DPX300 NMR spectrometer at 300.13 MHz (^{1}H) or at 75.47 MHz (^{13}C) in $CDCl_3$ solutions, unless stated otherwise. All chemical shifts were recorded in ppm relative to tetramethylsilane ($\delta = 0.0$ ppm). Spin–spin coupling constants (J value) recorded in Hz were measured directly from the spectra. Peak multiplicities were denoted by s (singlet); brs (broad singlet); d (doublet); brd (broad doublet); dd (doublet of doublets); ddd (doublet of doublet of doublets); t (triplet), and q (quartet). MS and HRMS were measured on a ThermoFinnigan MAT 95 KL at the Department of Chemistry, The Chinese University of Hong Kong, Hong Kong (China). Elemental analyses were carried out by MEDAC, Department of Chemistry, Brunel University, Cambridge (UK). All reactions were monitored by analytical TLC on Merck aluminum-precoated plates of silica gel 60 F254 with detection by spraying with 5% (w/v) dodecamolybdophosphoric acid in ethanol and subsequent heating. E. Merck silica gel 60 (230—400 mesh) was used for flash chromatography. All reagents and solvents were general reagent grade unless otherwise stated. Pyridine was distilled from barium oxide and stored in the presence of potassium hydroxide pellets. Methanol was dried by sodium and distilling from its sodium salt under nitrogen. DMF was dried by magnesium sulfate, filtered, and was then freshly distilled under reduced pressure. Acetonitrile was freshly distilled from P_2O_5 under nitrogen. THF was freshly distilled from Na/benzophenone ketyl under nitrogen. Dichloromethane was freshly distilled from P_2O_5 under nitrogen. Other reagents were purchased from commercial suppliers and were used without purification.

Enone 16: Cerium(III) chloride heptahydrate ($CeCl_3{\cdot}7H_2O$, 210 mg, 0.56 mmol) was added to a solution of enone **13** (120 mg, 0.48 mmol) in MeOH (10 mL) at 0°C. The resulting solution was stirred at 0°C for 30 min and then sodium borohydride ($NaBH_4$, 21 mg, 0.56 mmol) was added in portions over 15 min. After 30 min at 0°C, the reaction was quenched with saturated aq. NH_4Cl (5 mL). The aqueous phase was extracted with EtOAc (3×10 mL). The combined organic extracts were washed with brine (5 mL), dried ($MgSO_4$), and filtered. Concentration of the filtrate yielded crude alcohol **14**, which was used directly in the next reaction without further purification.

Triethylamine (Et_3N, 0.1 mL, 0.72 mmol) was added to a solution of the above crude alcohol **14** in dry CH_2Cl_2 (5 mL) at 0°C under N_2. *tert*-Butyldimethylsilyl trifluoromethanesulfonate (TBSOTf, 0.13 mL, 0.57 mmol) was added dropwise to the stirring solution at 0°C. The solution was then warmed to RT and stirred for a further 2 h under N_2. After this time, the reaction was quenched with saturated aq. NH_4Cl (5 mL) and the aqueous phase was extracted with CH_2Cl_2 (3×10 mL). The combined organic extracts were washed with brine (5 mL), dried ($MgSO_4$), and filtered. Concentration of the filtrate yielded crude silyl ether **15**, which was used in the next reaction without further purification.

Chromium trioxide (CrO_3, 960 mg, 9.6 mmol) and 3,5-dimethylpyrazole (920 mg, 9.6 mmol) were added to a solution of the above silyl ether **15** in CH_2Cl_2 (15 mL) at 0°C. The resulting solution was stirred for 24 h at RT and then diluted with Et_2O (20 mL), filtered through a thin pad of Celite, and the residue was eluted with EtOAc. Concentration of the filtrate followed by flash-column chromatography (*n*-hexane/Et_2O 4:1) afforded enone **16** (146 mg, 80%) as a white solid. Recrystallization from a mixture of *n*-hexane and EtOAc gave colorless crystals which were characterized by an X-ray crystallographic study. M.p. 92–94°C; $[\alpha] = -43.6$ ($c = 0.1$ in $CHCl_3$); $R_f = 0.61$ (*n*-hexane/EtOAc 2:1); IR (thin film): $\tilde{\nu} =$ 2928, 1664, 1544, 1071 cm^{-1}; ^{1}H NMR: $\delta = 0.20$ (s, 3H; $SiCH_3$), 0.23 (s, 3H; $SiCH_3$), 0.89 (s, 9H; *t*Bu), 1.42 (s, 3H; CH_3), 1.44 (s, 3H; CH_3), 1.76 (s, 3H; CH_3), 2.10 (s, 3H; CH_3), 2.84 (s, 1H), 3.52 (dd, 1H, $J = 2.1$,12.0 Hz; OCH_2), 3.60 (d, 1H, $J = 12.0$ Hz; OCH_2), 3.69 (d, 1H, $J =$ 12.0 Hz; OCH_2), 3.91 (dd, 1H, $J = 2.1$, 12.0 Hz; OCH_2), 4.52 (s, 1H; OCH), 4.92 (m, 1H; CH_2), 4.97 (m, 1H; CH_2), 5.94 ppm (m, 1H; CH); ^{13}C NMR: $\delta = -4.1$, −3.5, 19.2, 20.5, 22.7, 23.9, 26.4, 26.6, 27.9, 40.3, 57.6, 63.7, 69.1, 69.9, 98.7, 118.2, 127.4, 140.6, 158.5, 199.2 ppm; MS (EI): m/z: 380 $[M]^+$; HRMS (EI): calcd for $C_{21}H_{36}O_4Si$: 380.2377 $[M]^+$; found 380.2370.

Ketone 19: A solution of tetra-*n*-butylammonium fluoride (TBAF, 1.0 M) in THF (0.19 mL, 0.19 mmol) was added to a solution of **16** (60 mg, 0.16 mmol) in THF (5 mL) at RT under N_2. After 4 h at RT, the solution was diluted with Et_2O (5 mL), filtered through a thin pad of Celite and the residue was eluted with Et_2O. Concentration of the filtrate yielded crude alcohol **18,** which was then used directly in the next reaction without further purification.

Trifluoroacetic acid (TFA, 0.015 mL, 0.19 mmol) was added to a solution of the above crude alcohol **18** in dry CH_2Cl_2 (10 mL) at RT under N_2. After 15 min at RT, a solution of *p*-toluenesulfonic acid monohydrate (*p*TsOH·H_2O, 3 mg, 0.016 mmol) in 2,2-dimethoxypropane (0.10 mL, 0.80 mmol) was added and the resulting solution was stirred for 15 min at RT. The reaction was quenched with saturated aq. $NaHCO_3$ (10 mL). The aqueous phase was extracted with CH_2Cl_2 (3×10 mL). The combined organic extracts were washed with brine (5 mL), dried ($MgSO_4$), and filtered. Concentration of the filtrate followed by flash-column chromatography (*n*-hexane/Et_2O 2:1) gave ketone **19** (40 mg, 95%) as a white solid. Recrystallization from a mixture of *n*-hexane and EtOAc gave colorless crystals which were characterized by an X-ray crystallographic study. M.p. 160–162°C; $[\alpha] = -49.1$ ($c = 0.1$ in $CHCl_3$); $R_f = 0.68$ (*n*-hexane/EtOAc 1:1); IR (thin film): $\tilde{\nu} = 2918$, 1701, 1543, 1200 cm^{-1}; ^{1}H NMR: $\delta = 1.31$ (s, 3H; CH_3), 1.48 (s, 3H; CH_3), 1.54 (s, 3H; CH_3), 1.78 (s, 3H; CH_3), 2.52 (dd, 1H, $J = 1.2$, 16.8 Hz; OCH_2), 2.68 (d, 1H, $J = 16.8$ Hz; OCH_2), 3.03 (s, 1H; OCH), 3.48 (d, 1H, $J = 12.6$ Hz; OCH_2), 3.89 (d, 1H, $J = 12.6$ Hz; OCH_2), 4.11 (d, 1H, $J = 8.4$ Hz; OCH_2), 4.14 (s, 1H), 4.32 (dd, 1H, $J = 1.8$, 8.4 Hz; OCH_2), 4.77 (s, 1H; CH_2), 5.07 ppm (t, 1H, $J =$ .1.5 Hz; CH_2); ^{13}C NMR: $\delta = 19.0$, 19.2, 22.2, 29.7, 45.0, 54.3, 61.5, 64.5, 65.8, 70.0, 79.9, 82.1, 84.5, 98.7, 119.6, 138.6, 205.4 ppm; MS (EI): m/z: 266 $[M]^+$; HRMS (EI): calcd for $C_{15}H_{22}O_4$ 266.1513 $[M]^+$; found 266.1517.

Alcohol 24: Trifluoroacetic acid (TFA, 3.5 mL, 45.4 mmol) was added to a solution of **22** (10.0 g, 37.8 mmol) in dry CH_2Cl_2 (100 mL) at RT under N_2. After 15 min at RT, a solution of *p*-toluenesulfonic acid monohydrate (*p*TsOH·H_2O, 0.72 g, 3.8 mmol) in 2,2-dimethoxypropane (23.2 mL, 0.19 mol) was added and the resulting solution was stirred for 15 min at RT. The reaction was quenched with saturated aq. $NaHCO_3$ (100 mL). The aqueous phase was extracted with CH_2Cl_2 (3×50 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$), and filtered. Concentration of the filtrate followed by flash-column chromatography (*n*-hexane/Et_2O 4:1) gave alcohol **24** (9.1 g, 91%) as a white solid. Recrystallization from a mixture of *n*-hexane and EtOAc gave colorless crystals which were characterized by an X-ray crystallographic study. M.p. 102–103°C; $[\alpha] = +7.5$ ($c = 1.9$ in $CHCl_3$); $R_f = 0.79$ (*n*-hexane/EtOAc 4:1); IR (thin film): $\tilde{\nu} = 3484$, 2962, 1636, 1372 cm^{-1}; ^{1}H NMR: $\delta = 1.30$ (s, 3H; CH_3), 1.42 (s, 3H; CH_3), 1.48 (s, 3H; CH_3), 1.53 (ddd, 1H, $J = 1.5$, 4.8, 14.4 Hz), 1.72 (s, 3H; CH_3), 2.17 (s, 1H), 2.18 (dd, 1H, $J = 4.2$, 14.4 Hz), 2.51 (dd, 1H, $J = 4.5$, 13.5 Hz), 3.42 (d, 1H, $J = 12.6$ Hz; OCH_2), 3.79 (dd, 1H, $J = 1.5$, 4.2 Hz), 3.84 (d, 1H, $J = 12.6$ Hz; OCH_2), 4.04 (d, 1H, $J = 8.1$ Hz; OCH_2), 4.09 (s, 1H; OCH), 4.27 (d, 1H, $J =$ 8.1 Hz; OCH_2), 4.82 ppm (s, 2H; CH_2); ^{13}C NMR: $\delta = 15.9$, 18.8, 21.8, 29.5, 33.5, 44.7, 44.9, 60.8, 67.5, 74.5, 75.8, 85.5, 98.1, 114.2, 143.5 ppm; MS (EI): m/z: 269 $[M+H]^+$; elemental analysis calcd for $C_{15}H_{24}O_4$: C 67.14, H 9.01; found: C 67.43, H 9.18.

Tetracyclic acetate 41: Methylene blue (10 mg) was added to a solution of 1,3-diene acetate **40** (20 mg, 0.036 mmol) in toluene (4 mL) in a sealed tube. The solution was degassed and heated at 180°C (sand bath temperature) for 72 h. The reaction was cooled to RT, filtered through a thin pad of silica gel, and the residue was eluted with EtOAc. Concentration of the filtrate followed by flash-column chromatography (*n*-hexane/EtOAc 6:1) yielded *trans*-fused tetracyclic ketoacetate **41** (20 mg, 100%) as a colorless oil. $[\alpha] = +73.7$ ($c = 1.0$ in $CHCl_3$); $R_f = 0.52$ (*n*-hexane/EtOAc 5:1); IR (thin film): $\tilde{\nu} = 2930$, 1714, 1395 cm^{-1}; ^{1}H NMR: $\delta = 0.15$

(s, 3H; $SiCH_3$), 0.31 (s, 3H; $SiCH_3$), 0.98 (s, 9H; *t*Bu), 1.17 (s, 3H; CH_3), 1.19 (s, 3H; CH_3), 1.45 (d, 1H, $J=3.9$ Hz), 1.58 (brs, 1H), 1.96 (m, 3H), 1.99 (s, 3H; Ac), 2.22 (m, 3H), 2.77 (s, 3H; NCH_3), 2.88 (s, 3H; NCH_3), 4.15 (dd, 1H, $J=1.5$, 3.9 Hz; H-11), 4.25 (d, 1H, $J=7.5$ Hz; H-17), 4.95 (d, 1H, $J=1.5$ Hz; H-12), 5.08 (s, 1H, $J=7.5$ Hz; H-17), 5.36 (brs, 1H; H-3), 5.43 ppm (dd, 1H, $J=5.7$, 12.0 Hz; H-7); ^{13}C NMR: $\delta=-3.7$, -3.3, 14.8, 16.3, 18.6, 21.6, 21.9, 22.4, 26.4, 27.0, 34.3, 36.2, 37.0, 37.2, 46.6, 54.0, 56.0, 65.9, 69.6, 71.0, 82.9, 121.9, 133.0, 155.0, 170.0, 209.9 ppm; MS (FAB): *m/z*: 550 $[M+H]^+$; HRMS (FAB): calcd for $C_{29}H_{47}NO_7Si$: 550.3195 $[M+H]^+$; found 550.3200.

Alcohol 50: Potassium carbonate (K_2CO_3, 10 mg, 0.075 mmol) was added to a solution of pentacyclic enone **49** (50 mg, 0.075 mmol) in MeOH (3 mL) at RT. The reaction mixture was stirred for 4 h at RT and was then diluted with EtOAc. The mixture was filtered through a thin pad of silica gel and the residue was eluted with EtOAc. Concentration of the filtrate followed by flash-column chromatography (*n*-hexane/EtOAc 4:1) gave enone alcohol **50** (45 mg, 96%) as a colorless oil. $[\alpha]=+38.0$ ($c=0.5$ in $CHCl_3$); $R_f=0.48$ (*n*-hexane/EtOAc 2:1); IR (thin film): $\tilde{\nu}=3436$, 2930, 1770, 1742, 1664 cm^{-1}; ^{1}H NMR: $\delta=0.06$ (3H, s; $SiCH_3$), 0.08 (s, 3H; $SiCH_3$), 0.16 (s, 3H; $SiCH_3$), 0.20 (s, 3H; $SiCH_3$), 0.83 (s, 9H; *t*Bu), 0.94 (s, 9H; *t*Bu), 1.18 (s, 3H; CH_3), 1.30 (s, 3H; CH_3), 1.63 (m, 1H), 1.88 (s, 3H; CH_3), 2.05 (m, 1H), 2.13 (s, 3H; Ac), 2.80 (brs, 1H; OH), 3.10 (d, 1H, $J=3.9$ Hz; H-9), 3.25 (brd, 1H, $J=12.9$ Hz; H-5), 3.68 (dd, 1H, $J=0.9$, 7.8 Hz; H-17), 3.84 (d, 1H, $J=2.4$ Hz; H-12), 3.85 (s, 1H; H-1), 4.24 (dd, 1H, $J=2.4$, 3.9 Hz; H-11), 4.81 (d, 1H, $J=7.8$ Hz; H-17), 5.46 (t, 1H, $J=2.7$ Hz; H-7), 5.90 ppm (m, 1H; H-3); ^{13}C NMR: $\delta=-4.8$, -3.2, -3.0, -2.8, 15.7, 17.1, 18.2, 18.7, 21.7, 23.3, 25.8, 26.4, 28.2, 38.5, 40.9, 44.2, 50.9, 68.8, 69.0, 72.9, 76.0, 78.8, 81.0, 124.6, 164.4, 171.0, 197.6, 205.8 ppm; MS (EI): *m/z*: 622 $[M]^+$; HRMS (EI): calcd for $C_{32}H_{54}O_8Si_2$: 622.3352 $[M]^+$; found: 622.3343.

Alcohol 52: 1,1,1-Triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1*H*)-one (Dess–Martin periodinane, 16 mg, 0.038 mmol)[27] was added to a solution of **50** (20 mg, 0.032 mmol) in dry CH_2Cl_2 (2 mL) at RT under N_2. The reaction mixture was stirred for 4 h at RT under N_2 and then was quenched with saturated aq. $NaHCO_3$ (3 mL). The aqueous phase was extracted with CH_2Cl_2 (3×5 mL). The combined organic extracts were washed with brine (3 mL), dried ($MgSO_4$), and filtered. Concentration of filtrate yielded crude triketone **51,** which was then directly used in the next reaction without further purification.

Sodium borohydride ($NaBH_4$, 1.2 mg, 0.032 mmol) was added to a solution of the above crude triketone **51** in THF (4.5 mL) and MeOH (0.5 mL) at 0°C. After 1 h at 0°C, the reaction was quenched with saturated aq. NH_4Cl (1 mL). The aqueous phase was extracted with EtOAc (3×5 mL). The combined organic extracts were washed with brine (2 mL), dried ($MgSO_4$), and filtered. Concentration of the filtrate followed by flash-column chromatography (*n*-hexane/EtOAc 4:1) yielded **52** (17 mg, 85%) as a colorless oil: $[\alpha]=+22.0$ ($c=0.5$ in $CHCl_3$); $R_f=0.50$ (hexane/EtOAc 2:1); IR (thin film): $\tilde{\nu}=3433$, 2934, 1770, 1743, 1672 cm^{-1}; ^{1}H NMR: $\delta=0.06$, (s, 3H; $SiCH_3$), 0.09 (s, 3H; $SiCH_3$), 0.13 (s, 3H; $SiCH_3$), 0.16 (s, 3H; $SiCH_3$), 0.84 (s, 9H; *t*Bu), 0.92 (s, 9H; *t*Bu), 1.18 (s, 3H; CH_3), 1.60 (ddd, 1H, $J=2.1$, 12.3, 14.1 Hz; H-6), 1.90 (s, 3H; CH_3), 2.02 (ddd, 1H, $J=2.4$, 3.6, 14.1 Hz; H-6), 2.14 (s, 3H; Ac), 2.52 (d, 1H, $J=3.6$ Hz; H-9), 3.03 (brd, 1H, $J=11.7$ Hz; H-5), 3.64 (dd, 1H, $J=0.9$, 7.5 Hz; H-17), 3.82 (d, 1H, $J=2.7$ Hz; H-12), 4.00 (s, 1H; H-1), 4.14 (d, 1H, $J=0.9$ Hz; OH), 4.86 (d, 1H, $J=7.5$ Hz; H-17), 4.92 (dd, 1H, $J=2.7$, 3.6 Hz; H-11), 5.46 (dd, 1H, $J=2.1$, 3.6 Hz; H-7), 6.07 ppm (q, 1H, $J=1.2$ Hz; H-3); ^{13}C NMR: $\delta=-4.8$, -3.6, -3.4, -2.9, 11.5, 16.8, 18.3, 18.9, 21.7, 23.5, 25.9, 26.4, 27.7, 43.9, 48.6, 49.2, 51.0, 69.0, 69.2, 75.2, 79.3, 81.0, 84.4, 124.5, 165.1, 170.7, 198.4, 205.8 ppm; MS (EI): *m/z*: 622 $[M]^+$; HRMS (EI): calcd for $C_{32}H_{54}O_8Si_2$: 622.3352 $[M]^+$; found 622.3351.

Lactone 53: A solution of tetracyclic keto-acetate **52** (5 mg, 8.0 μmol) in dry THF (0.4 mL) was added to a solution of lithium diisopropylamide (LDA, 0.3 M) in dry THF (0.2 mL, 0.060 mmol) dropwise at −78°C under N_2. The resulting solution was stirred for 30 min at −78°C under N_2. The reaction was quenched with saturated aq. NH_4Cl (0.5 mL). The aqueous phase was extracted with EtOAc (3×3 mL). The combined organic extracts were washed with brine (1 mL), dried ($MgSO_4$), and filtered. Concentration of the filtrate followed by flash-column chromatography (*n*-hexane/EtOAc 4:1) gave pentacyclic lactone **53** (3 mg) as a white solid with starting material **52** (1 mg) recovered (80% based on 80% conversion). M.p. 203–204°C; $[\alpha]=+31.7$ ($c=0.5$ in $CHCl_3$); $R_f=0.52$ (*n*-hexane/EtOAc 2:1); IR (thin film): $\tilde{\nu}=3428$, 2926, 1739, 1103 cm^{-1}; ^{1}H NMR: $\delta=0.15$ (s, 3H; $SiCH_3$), 0.17 (s, 3H; $SiCH_3$), 0.19 (s, 3H; $SiCH_3$), 0.20 (s, 3H; $SiCH_3$), 0.89 (s, 9H; *t*Bu), 0.90 (s, 9H; *t*Bu), 0.99 (s, 3H; CH_3), 1.28 (s, 3H; CH_3), 1.82–1.91 (m, 1H), 1.96 (s, 3H; CH_3), 2.37–2.43 (m, 1H), 2.54 (dd, 1H, $J=2.4$, 14.4 Hz; H-15), 2.69 (brd, 1H, $J=15.9$ Hz; H-5), 2.78 (d, 1H, $J=14.4$ Hz; H-15), 2.79 (d, 1H, $J=3.3$ Hz; H-9), 3.58 (d, 1H, $J=8.1$ Hz; H-17), 3.72 (d, 1H, $J=1.5$ Hz; H-12), 4.09 (s, 1H; H-1), 4.10 (s, 1H; OH), 4.45 (d, 1H, $J=4.8$ Hz; H-7), 4.97 (dd, 1H, $J=1.5$, 3.3 Hz), 5.18 (d, 1H, $J=8.1$ Hz), 6.09 (q, 1H, $J=1.5$ Hz), 6.19 ppm (d, 1H, $J=2.4$ Hz; OH); ^{13}C NMR: $\delta=-4.5$, -3.6, -2.9, 11.2, 18.5, 18.9, 23.1, 26.2, 26.6, 27.4, 29.8, 30.2, 38.3, 44.5, 44.7, 46.4, 46.6, 75.8, 76.7, 78.3, 78.7, 82.8, 83.5, 83.6, 124.8, 163.0, 173.3, 198.5 ppm; MS (EI): *m/z*: 592 $[M]^+$; HRMS (EI): calcd for $C_{32}H_{56}O_6Si_2$: 592.3610 $[M]^+$; found: 592.3600.

(−)-14-*epi*-Samaderine E (5): Deionized water (0.5 mL) was added to a solution of pentacyclic lactone **53** (5 mg, 8.0 μmol) in trifluoroacetic acid (TFA, 1 mL) at RT under N_2. The reaction mixture was stirred for 24 h at RT under N_2. Concentration of the solution under vacuum followed by flash-column chromatography (*n*-hexane/EtOAc/MeOH 10:9:1) afforded **5** (2.2 mg, 71%) as a white solid. Recrystallization from a mixture of EtOAc and MeOH gave white prisms. M.p. 230–232°C; $[\alpha]=-11.9$ ($c=0.1$ in pyridine); $R_f=0.29$ (*n*-hexane/EtOAc/MeOH 4:3:1); IR (thin film): $\tilde{\nu}=3374$, 2914, 1674, 1445 cm^{-1}; ^{1}H NMR (CD_3OD): $\delta=1.04$ (s, 3H; CH_3), 1.30 (s, 3H; CH_3), 1.98 (s, 3H; CH_3), 2.09 (ddd, 1H, $J=6.0$, 13.8, 15.6 Hz; H-6), 2.35 (ddd, 1H, $J=0.9$, 3.3, 15.6 Hz; H-6), 2.64 (d, 1H, $J=14.4$ Hz; H-15), 2.76 (brd, 1H, $J=12.9$ Hz; H-5), 2.77 (brd, 1H, $J=3.3$ Hz; H-9), 2.77 (d, 1H, $J=14.4$ Hz; H-15), 3.66 (d, 1H, $J=0.6$ Hz; H-12), 3.73 (dd, 1H, $J=1.2$, 8.4 Hz; H-17), 4.28 (s, 1H; H-1), 4.62 (d, 1H, $J=6.0$ Hz; H-7), 4.65 (d, 1H, $J=4.5$ Hz; H-11), 4.96 (d, 1H, $J=8.4$ Hz; H-17), 6.04 ppm (q, 1H, $J=1.5$ Hz; H-3); ^{13}C NMR (CD_3OD): $\delta=11.2$, 13.9, 17.5, 20.7, 22.4, 26.7, 28.3, 38.5, 45.9, 46.1, 47.0, 47.5, 54.0, 54.8, 75.4, 76.3, 79.4, 79.7, 81.9, 83.2, 83.5, 125.1, 165.0, 176.2, 200.4 ppm; MS (CI): *m/z*: 395 $[M+H]^+$; HRMS (CI): calcd for $C_{20}H_{26}O_8$: 395.1700 $[M+H]^+$; found 395.1710.

Acknowledgement

This work was supported by financial support from the CUHK direct grant. We thank Prof. M. Kobayashi (Osaka University) for kindly providing the ^{1}H and ^{13}C NMR spectra of natural (−)-samaderine Y for comparison.

[1] a) J. Polonsky, *Prog. Chem. Org. Nat. Prod.* **1985**, *47*, 221–264; b) P. A. Grieco, E. D. Moher, M. Seya, J. C. Huggman, J. H. Grieco, *Phytochemistry* **1994**, *37*, 1451–1454; c) M. Ishibashi, T. Tsuyuki, T. Murae, H. Hiroto, T. Takahashi, A. Itai, Y. Iitaka, *Bull. Chem. Soc. Jpn.* **1983**, *56*, 3683–3693; d) M. C. Wani, H. L. Taylor, M. E. Wall, A. T. McPhail, K. D. Onan, *J. Chem. Soc. Chem. Commun.* **1977**, 295–297; e) H. Aono, K. Koike, J. Kanako, T. Ohmoto, *Phytochemistry* **1994**, *37*, 579–584; f) I. Kitagawa, T. Mahmud, K. I. Yokota, S. Nakagawa, T. Mayumi, M. Kobayashi, H. Shibuya, *Chem. Pharm. Bull.* **1996**, *44*, 2009–2014.

[2] For recent review: Z. Guo, S. Vangapandu, R. W. Sindelar, L. A. Walker, R. D. Sindelar, *Curr. Med. Chem.* **2005**, *12*, 173–190.

[3] a) E. D. Moher, P. A. Grieco, J. L. Collins, *J. Org. Chem.* **1993**, *58*, 3789–3790; b) E. D. Moher, J. L. Collins, P. A. Grieco, *J. Am. Chem. Soc.* **1992**, *114*, 2764–2765.

[4] T. K. M. Shing, X. Y. Zhu. Y. Y. Yeung, *Chem. Eur. J.* **2003**, *9*, 5489–5500.

[5] T. K. M. Shing, Y. Y. Yeung, *Angew. Chem.* **2005**, *117*, 8195–8198; *Angew. Chem. Int. Ed.* **2005**, *44*, 7981–7984.

[6] a) T. K. M. Shing, Y. Tang, *J. Chem. Soc. Chem. Commun.* **1992**, 341–342; b) T. K. M. Shing, Y. Tang, *J. Chem. Soc. Perkin Trans. 1* **1994**, 1625–1631; c) T. K. M. Shing, Q. Jiang, *J. Org. Chem.* **2000**, *65*, 7059–7069.
[7] a) A. L. Gemal, J. L. Luche, *J. Am. Chem. Soc.* **1981**, *103*, 5454–5459; b) A. Krief, D. Surleraux, N. Ropson, *Tetrahedron: Asymmetry* **1993**, *4*, 289–293.
[8] W. G. Salmond, M. A. Barta, J. L. Havens, *J. Org. Chem.* **1978**, *43*, 2057–2059.
[9] CCDC-226340 (**16**), -232925 (**19**), -235459 (**29**), -266924 (**49**), -281817 (**54**), and -279945 (**57**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
[10] J. Katsuhara, *Bull. Chem. Soc. Jpn.* **1969**, *42*, 2391–2394.
[11] H. Takikawa, K. Isono, M. Sasaki, F. A. Macías, *Tetrahedron Lett.* **2003**, *44*, 7023–7025.
[12] J. Q. Yu, E. J. Corey, *J. Am. Chem. Soc.* **2003**, *125*, 3232–3233.
[13] A. J. Catino, R. E. Forslund, M. P. Doyle, *J. Am. Chem. Soc.* **2004**, *126*, 13622–13623.
[14] Q. Jiang, T. K. M. Shing, *Tetrahedron Lett.* **2001**, *42*, 5271–5273.
[15] a) W. P. Griffith, S. V. Ley, G. P. Whitcombe, A. D. White, *J. Chem. Soc. Chem. Commun.* **1987**, 1625–1627; b) S. V. Ley, J. Norman, W. P. Griffith, S. P. Marsden, *Synthesis* **1994**, 639–666.
[16] a) S. R. Wilson, D. T. Mao, K. M. Jernberg, S. T. Ezmirly, *Tetrahedron Lett.* **1977**, *18*, 2559–2562; b) M. T. Zoeckler, B. K. Carpenter, *J. Am. Chem. Soc.* **1981**, *103*, 7661–7663.
[17] D. F. Taber, S. A. Saleh, *Tetrahedron Lett.* **1982**, *23*, 2361–2364.
[18] a) K. A. Parker, T. Iqbal, *Tetrahedron Lett.* **1986**, *27*, 6291–6294; b) S. R. Wilson, D. T. Mao, *J. Am. Chem. Soc.* **1978**, *100*, 6289–6291; c) W. R. Roush, *J. Am. Chem. Soc.* **1980**, *102*, 1390–1404; d) K. A. Parker, T. Iqbal, *J. Org. Chem.* **1987**, *52*, 4369–4377.
[19] T. K. M. Shing, T. Y. Li, S. H. L. Kok, *J. Org. Chem.* **1999**, *64*, 1941–1946.
[20] a) A. J. Pearson, G. R. Han, *J. Org. Chem.* **1985**, *50*, 2791–2792; b) A. J. Pearson, Y. Chen, S. Hsu, T. Ray, *Tetrahedron Lett.* **1984**, *25*, 1235–1238.
[21] T. K. M. Shing, Y.-Y. Yeung, P. L. Su, *Org. Lett.* **2006**, *8*, 3149–3151.
[22] a) G. J. Williams, N. R. Hunter, *Can. J. Chem.* **1976**, *54*, 3830–3832; b) R. C. Cambie, M. P. Hay, L. Larsen, C. E. F. Rickard, P. S. Rutledge, P. D. Woodgate, *Aust. J. Chem.* **1991**, *44*, 821–842; c) B. B. Snider, L. Han, C. Xie, *J. Org. Chem.* **1997**, *62*, 6978–6984.
[23] D. D. Long, M. D. Smith, A. Martín, J. R. Wheatley, D. G. Watkin, M. Müller, G. W. J. Fleet, *J. Chem. Soc. Perkin Trans. 1* **2002**, 1982–1998.
[24] J. Kaulen, *Angew. Chem.* **1987**, *99*, 800-802; *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 773–774.
[25] O. Mitsunobu, *Synthesis* **1981**, 1–28.
[26] R. F. Spohn, P. A. Grieco, R. P. Nargund, *Tetrahedron Lett.* **1987**, *28*, 2491–2494.
[27] a) D. B. Dess, J. C. Martin, *J. Org. Chem.* **1983**, *48*, 4155–4156; b) D. B. Dess, J. C. Martin, *J. Am. Chem. Soc.* **1991**, *113*, 7277–7287; c) R. E. Ireland, L. Liu, *J. Org. Chem.* **1993**, *58*, 2899; d) M. Frigerio, M. Santagostino, S. Sputore, *J. Org. Chem.* **1999**, *64*, 4537–4538.
[28] H. F. Chow, D. Seebach, *Helv. Chim. Acta* **1986**, *69*, 604–614.
[29] A. J. Reynolds, A. J. Scott, C. I. Turner, M. S. Sherburn, *J. Am. Chem. Soc.* **2003**, *125*, 12108–12109.
[30] a) A. K. Sinhababu, M. Kawase, R. T. Borchardt *Synthesis* **1998**, *9*, 710–712; b) W. Zhang, M. J. Robins, *Tetrahedron Lett.* **1992**, *33*, 1177–1180.
[31] S. Kawahara, T. Wada, M. Sekine, *Tetrahedron Lett.* **1996**, *37*, 509–512.
[32] F. Zanardi, L. Battistini, L. Marzocchi, D. Acquotti, G. Rassu, L. Pinna, L. Auzzas, V. Zambrano, G. Casiraghi, *Eur. J. Org. Chem.* **2002**, 1956–1965.
[33] D. R. Kelly, S. M. Roberts, R. F. Newton, *Synth. Commun.* **1979**, *9*, 295–299.
[34] R. F. Newton, D. P. Reynolds, M. A. W. Finch, D. R. Kelly, S. M. Roberts, *Tetrahedron Lett.* **1979**, *20*, 3981–3982.
[35] I. D. Spiers, S. Freeman, D. R. Poyner, C. H. Schwalbe, *Tetrahedron Lett.* **1995**, *36*, 2125–2128.
[36] S. Bernstein, J. J. Brown, L. I. Feldman, N. E. Rigler, *J. Am. Chem. Soc.* **1959**, *81*, 4956–4962.
[37] a) H. C. Brown, C. A. Brown, *J. Am. Chem. Soc.* **1963**, *85*, 1005–1006; b) C. A. Brown, V. K. Ahuja, *J. Org. Chem.* **1973**, *38*, 2226–2230.
[38] a) M. Fetizon, M. Golfier, *C. R. Acad. Sci. Ser. C* **1968**, *267*, 900–903; b) M. Fetizon, M. Golfier, J. M. Louis, *J. Chem. Soc. D* **1969**, *19*, 1102; c) M. Fetizon, M. Golfier, P. Mourgues, *Tetrahedron Lett.* **1972**, *13*, 4445–4448.

Received: May 13, 2006
Published online: August 22, 2006

