Total Synthesis of (+)-Quassin

Tony K. M. Shing* and Qin Jiang

Department of Chemistry, The Chinese University of Hong Kong, Shatin, Hong Kong

tonyshing@cuhk.edu.hk

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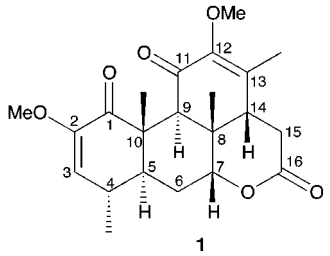
A total synthesis of (+)-quassin from naturally occurring (*S*)-(+)-carvone is described. The total number of steps was 28, and the overall yield was about 2.6%. The synthetic strategy for the construction of the tetracyclic carbon framework was based on a C→ABC→ABCD ring annulation sequence, involving an aldol reaction, an intramolecular Diels−Alder reaction, and an intramolecular acylation as the key steps. Subsequent functionalization of ring A and ring C then afforded the target (+)-quassin.

Introduction

Quassinoids, a large and constantly expanding family of terpenoid bitter principles found in Simaroubaceae, have been used as folk medicine for centuries in the treatment of cancer in Asia and Africa.[1] In 1937, Clark[2] reported the isolation of the first bitter principle, quassin (**1**), and Robertson et al.[3] succeeded in characterizing it in the 1950s. A decade later, Valenta and co-workers[4] established its constitution and stereochemistry. Since the structure of quassin was disclosed, numerous highly oxygenated quassinoids have been isolated and characterized.[5] Most quassinoids have either a tetracyclic or a pentacyclic C_{20} carbon framework comprising a number of contiguous stereocenters. However, there had been no systematic investigation into the chemotherapeutic potential of quassinoids before the report in 1970 by Wall and Wani.[6] Since then, a wide spectrum of biological activities have been revealed, including in vivo antineoplastic, antiviral, antimalarial, antifeedant, antiamoebic, antituberculosis, and insecticidal properties.[7]



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The extensive biological activities and the intriguing structures of quassinoids have attracted immense interest from synthetic chemists.[8] However, the first total synthesis of racemic quassin (**1**) was only realized in 1980 by the impressive Grieco group.[9] Starting from Wieland−Miescher ketone,[10] (±)-quassin (**1**) was synthesized in 23 steps and the total yield was less than 0.89%. The C(8) quaternary center and the C(14) stereocenter were secured by a Lewis acid-catalyzed intermolecular Diels−Alder reaction. In 1991, Valenta and co-workers[11] reported another total synthesis of (±)-quassin (**1**) in which the number of steps was 25 with a overall yield of about 0.14%. To date, there is only one report on the synthesis of optically active (+)-quassin (**1**), which was addressed by the Watt group[12] using the (−)-enantiomer of the

* To whom correspondence should be addressed. Phone: (852)-2609 6367. Fax: (852)-2603 5057.

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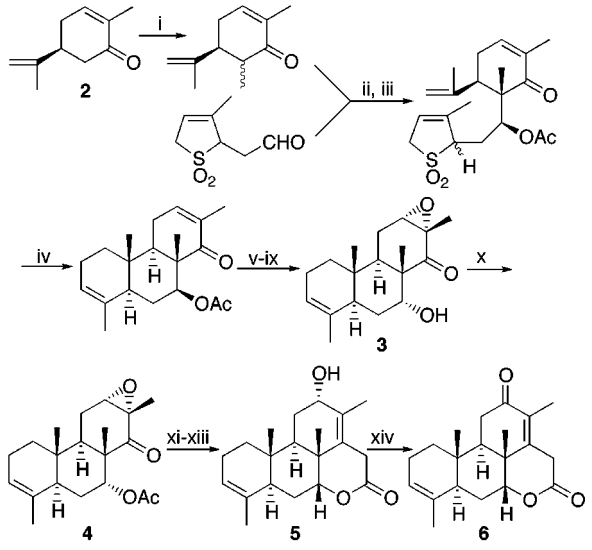
Scheme 1[a]



[a] Key: (i) LDA, THF, −30 °C; CH_3I (88%); (ii) LDA, THF, DMPU, −78 °C (87%); (iii) Ac_2O, pyridine, DMAP (cat.), CH_2Cl_2, rt (89%); (iv) PhCN, methylene blue, reflux (62%); (v) 40% Triton B, 70% TBHP, THF, rt; (vi) KOH, MeOH, rt [85% for steps (v) and (vi)]; (vii) Tf_2O, pyridine, DMAP (cat.), CH_2Cl_2, rt; (viii) wet DMF, rt; (ix) K_2CO_3, MeOH, rt [85% for steps from (vii) to (ix)]; (x) Ac_2O, pyridine, DMAP (cat.), CH_2Cl_2, rt (100%); (xi) LDA, THF, DMPU, −78 °C to 0 °C (98%); (xii) $SOCl_2$, pyridine, 0 °C (98%); (xiii) $NaBH_4$, $NiCl_2{\cdot}6H_2O$ (cat.), MeOH, −25 °C (53%); (xiv) PCC, 3 Å molecular sieves, CH_2Cl_2, rt (90%).

Wieland−Miescher ketone as the starting material. The number of steps was 35 with a less than 0.02% overall yield. The crucial steps included an intermolecular Diels−Alder reaction and a free radical cyclization of an α-bromoacetal to form ring D.

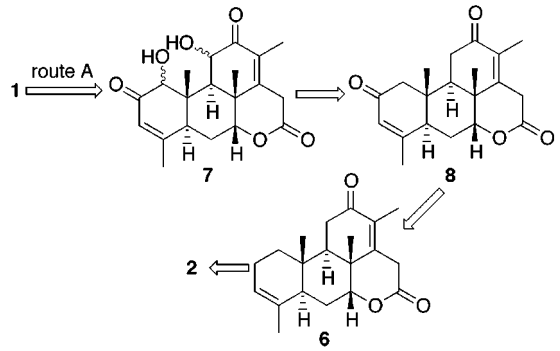
In our own quest for an enantiospecific route toward tetracyclic quassinoids such as (+)-quassin (**1**), we already disclosed the construction of a tetracyclic quassinoid skeleton **6** which has the general ABCD ring system with five stereogenic centers common to numerous quassinoids.[13] Starting from (*S*)-(+)-carvone (**2**), the synthetic strategy based on a C → ABC → ABCD ring annulation sequence was executed. The crucial steps included (i) a stereoselective aldol reaction, (ii) an endo-selective intramolecular Diels−Alder reaction, and (iii) a stereoselective aldol cyclization. As an extension of this approach, we now report our successful total synthesis of (+)-quassin.[14]

Results and Discussion

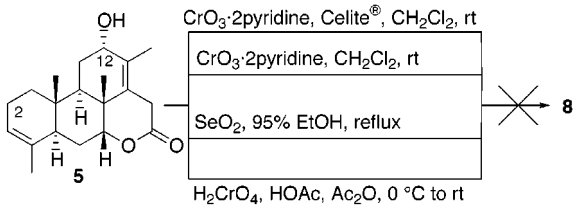
Our recent endeavor[13d] has described that (+)-carvone (**2**) could be readily converted into tetracycle **6** as shown in Scheme 1. With this series of compounds in hand, we could explore the functionalization of the skeleton to complete the construction of the target molecule, (+)-quassin (**1**).

To reduce the number of synthetic steps and make the synthesis more efficient, we designed a synthetic strategy (Scheme 2) in which the functionalization of ring A and ring C might be achieved at the same time. The crucial steps would include (i) an allylic oxidation at C(2) and (ii) a one-pot oxygenation at C(1) and C(11). Toward this end, we planned to execute the allylic oxidation at C(2) first.

Scheme 2



Scheme 3



Starting from the tetracyclic alcohol **5**, we attempted various oxidative conditions such as (i) $CrO_3{\cdot}$pyridine complex in CH_2Cl_2,[15] (ii) SeO_2 in EtOH under reflux,[16] and (iii) H_2CrO_4 in HOAc−Ac_2O[17] to oxidize the C(12) hydroxy group to ketone and the allylic methylene at C(2) to enone (Scheme 3). Unfortunately, all these oxidative conditions failed to give the desired dienone **8**. The tetracyclic enone **6** could be isolated initially under conditions (i) and (iii), but was destroyed upon longer reaction time. Under conditions (ii), the tetracyclic alcohol **5** disintegrated.

After the fruitless allylic oxidation of alcohol **5**, we subjected the tetracyclic enone **6** to other kinds of oxidative conditions such as (i) PDC and 70% *tert*-butyl hydroperoxide (TBHP) aqueous solution in benzene,[18] (ii) $CrO_3{\cdot}$3,5-dimethylpyrazole (3,5-DMP) complex in CH_2Cl_2,[19] and (iii) $Cr(CO)_6$ and 70% TBHP in CH_3CN under reflux[20] (Scheme 4). Under conditions (i) or (ii), the tetracyclic enone **6** decomposed. The conditions (iii) gave a very poor yield (8%) of dienone **8**. The reason for this is probably due to the instability of the lactone D ring, which could not survive the vigorous oxidation conditions.

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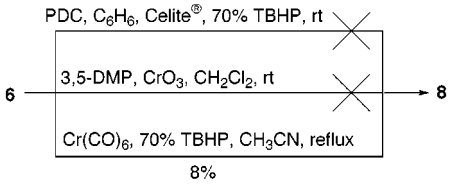
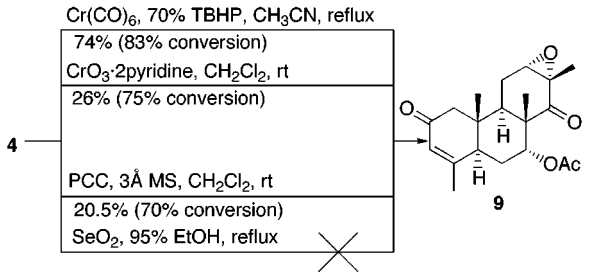
Scheme 4



Scheme 5



Since the lactone ring was speculated to be unstable, we therefore chose the tricyclic keto ester **4** for the allylic oxidation. Various oxidations were then attempted and the best yield of enone **9** (74%, 83% conversion) was provided by using $Cr(CO)_6$ and 70% TBHP in CH_3CN under reflux (Scheme 5).

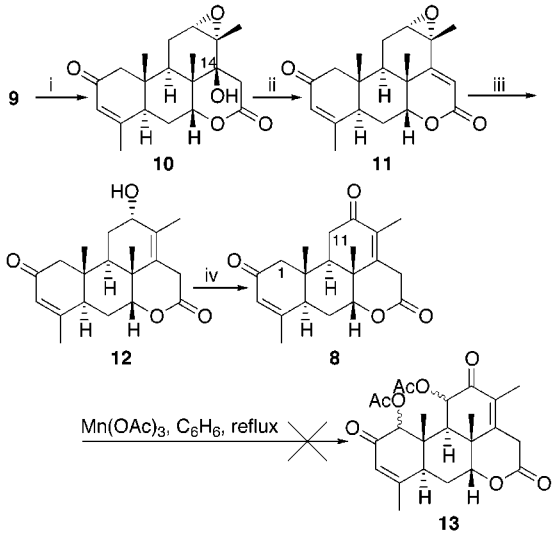
The enone **9** was subjected to LDA in THF at −78 to 0 °C to induce a stereoselective intramolecular aldol cyclization. Indeed, the lactone **10** was isolated in 95% yield as a single diastereomer. The cyclization of **9** would undergo a favorable α-axial attack to give a *β*-face hydroxy group at C(14) in lactone **10**. Dehydration of **10** using $SOCl_2$ in pyridine at 0 °C gave the α,*β*-unsaturated lactone **11** in 98% yield. Reduction of **11** with $NaBH_4$ in the presence of a catalytic amount of $NiCl_2 \cdot 6H_2O$ at −35 °C furnished the alcohol **12** in 60% yield. Subsequently, the alcohol **12** was oxidized with CrO_3·pyridine complex, affording the dienone **8** in 83% yield. We were now in the stage of the one-pot oxygenation at C(1) and C(11). Manganic acetate had been proved to be an efficient reagent for α-acetoxylation of enones.[12,21] Thus, the dienone **8** was treated with $Mn(OAc)_3$ in dry benzene under reflux using a Dean−Stark apparatus for separation of the water of crystallization in manganic acetate (Scheme 6). Unfortunately, the starting material **8** was completely consumed, and the desired diacetate **13** was not detectable. Again, the unstable lactone ring could not survive this oxygenation.

The failure of route A forced us to design another synthetic avenue for the functionalization of ring A and ring C. Thus, the synthetic route B (Scheme 7) would be studied.

In route B, for the purpose of avoiding the destruction of the lactone ring, functionalization of ring A and ring C should be manipulated separately. The oxygenation of ring A would be completed before the closure of ring D. Thus, a sequence of chemical transformations involving (i) functionalization of ring A, (ii) cyclization of ring D, and (iii) functionalization of ring C should be employed.

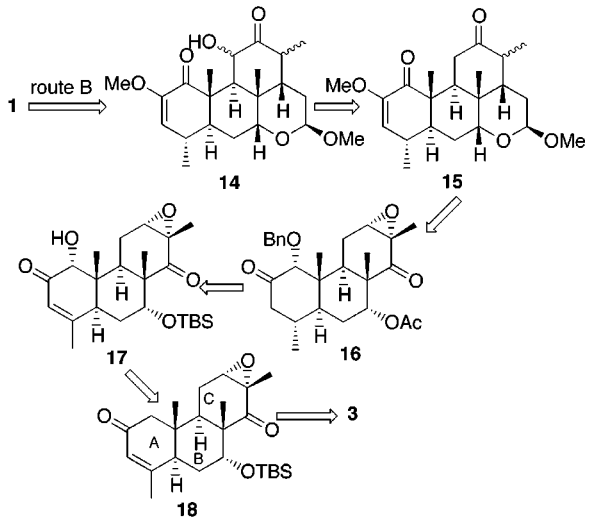
The functionalization of ring A focused on an allylic oxidation at C(2) and an oxygenation at C(1). The

Scheme 6[a]



[a] Key: (i) LDA, THF, −78 °C to 0 °C (95%); (ii) $SOCl_2$, pyridine, 0 °C (98%); (iii) $NaBH_4$, $NiCl_2 \cdot 6H_2O$, MeOH, −35 °C (60%); (iv) CrO_3·2pyridine, CH_2Cl_2, rt (83%).

Scheme 7



α-alcohol **3** was selected as the starting material (Scheme 8). Protection of the C(7α) hydroxy group in **3** with TBDMSOTf in 2,6-lutidine afforded the silyl ether **19** in 98% yield (75% conversion). Treatment of **19** with $Cr(CO)_6$ and 70% TBHP in CH_3CN under reflux completed the regioselective allylic oxidation to give the enone **18** as the major product in 78% yield (84% conversion). Stereoselective acetoxylation at C(1) of enone **18** with $Mn(OAc)_3$ furnished successfully the desired α-acetate **20** as the sole product in 84% yield. The steric hindrance of the *β*-face methyl group at C(10) caused the acetoxylation to occurr at the α-face, affording an α-face acetate at C(1) in **20** (Figure 1). The constitution and stereochemistry of **20** was confirmed by an X-ray crystallographic analysis.[14] Deacetylation of acetate **20** produced the alcohol **17** in 87% yield. Stereoselective hydrogenation of **17** provided the keto alcohol **21** in essentially quantitative yield. The steric hindrance of the α-face proton at C(5) directed the hydrogen to approach the alkene moiety from the less hindered *β*-face to give an α-face methyl group

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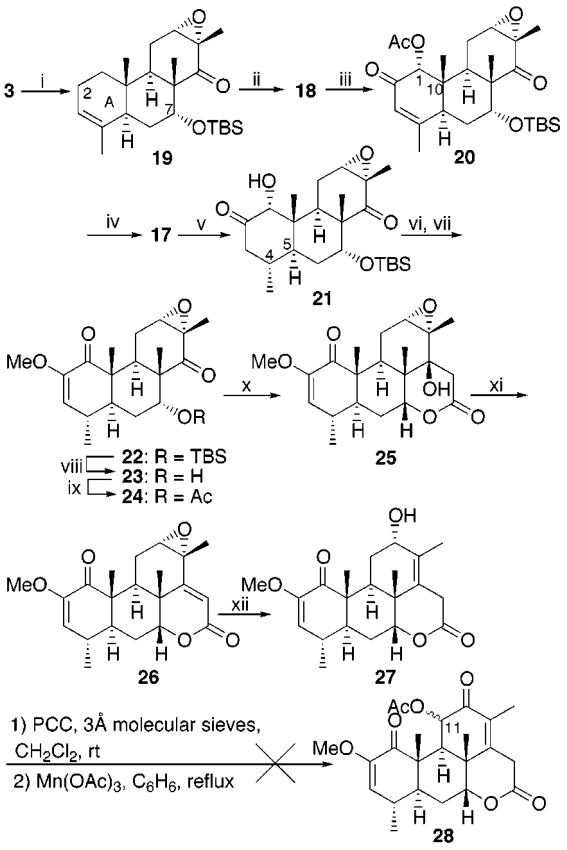
Scheme 8[a]



[a] Key: (i) TBSOTf, 2,6-lutidine, rt, 5 days (98% yield based on 75% conversion); (ii) $Cr(CO)_6$, 70% TBHP, CH_3CN, reflux (78% yield based on 84% conversion); (iii) $Mn(OAc)_3$, C_6H_6, reflux (84%); (iv) K_2CO_3, MeOH, rt (87%); (v) H_2, 10% Pd/C, EtOH, rt (99%); (vi) DMSO, TFAA, CH_2Cl_2, −78 °C then Et_3N, −78 °C to rt (97%); (vii) NaH, CH_3I, DMF, −20 °C (97%); (viii) TBAF, THF, 50 °C (95% yield based on 90% conversion); (ix) Ac_2O, DMAP, CH_2Cl_2, rt (89%); (x) LDA, THF, −78 °C (73% yield based on 73% conversion); (xi) $SOCl_2$, pyridine, 0 °C (95%); (xii) $NaBH_4$, $NiCl_2 \cdot 6H_2O$, MeOH, −35 °C (30%).

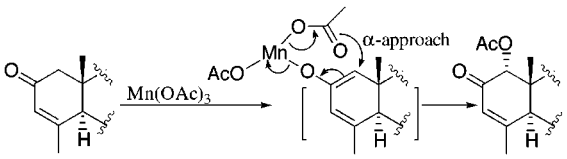


Figure 1.

at C(4) in **21**. Swern oxidation[22] of **21** followed by *O*-methylation produced the α-methoxy enone **22** in an excellent yield. In this way, the A ring was completely functionalized. Assembly of ring D and subsequent functionalization of ring C would be the new mission.

Desilylation of α-methoxy enone **22** with tetra-*n*-butylammonium fluoride (TBAF) in THF at 50 °C gave the alcohol **23** which was acylated to the acetate **24** in good yield. Treatment of acetate **24** with LDA in THF at −78 °C allowed the closure of D ring to give the lactone **25** as a single diastereomer in good yield. Dehydration of **25** gave the α,*β*-unsaturated lactone **26** in 95% yield. Reduction of **26** with $NaBH_4$ in the presence of a catalytic amount of $NiCl_2 \cdot 6H_2O$ furnished the alcohol **27** in poor

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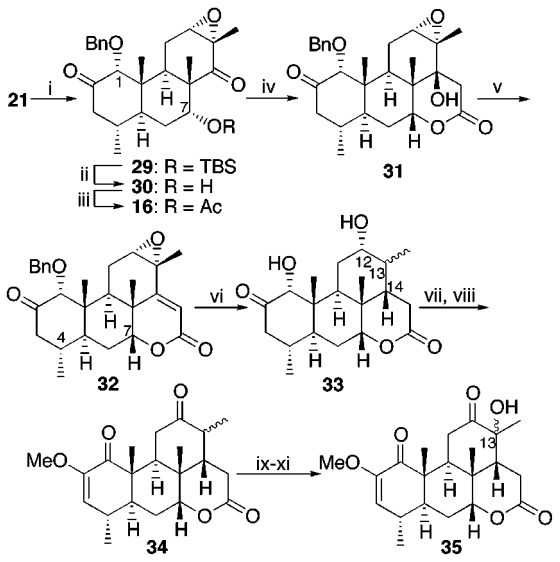
Scheme 9[a]



[a] Key: (i) NaH, THF, BnBr, TBAI (cat.), 0 °C to rt (85%); (ii) $Et_2O \cdot BF_3$, CH_2Cl_2, 0 °C to 10 °C (92%); (iii) Ac_2O, DMAP, CH_2Cl_2, rt (94%); (iv) LDA, THF, −78 °C (90%); (v) $SOCl_2$, pyridine, 0 °C (94%); (vi) H_2, 10% Pd/C, EtOH, rt (92%); (vii) DMSO, TFAA, CH_2Cl_2, −78 °C then Et_3N, −78 °C to rt (94%); (viii) NaH, CH_3I, DMF, −20 °C (94%); (ix) Et_3N, TMSOTf, CH_2Cl_2, −10 °C; (x) *m*CPBA, $NaHCO_3$, CH_2Cl_2, −20 °C, (xi) TBAF [62% yield for steps from (ix) to (xi)].

yield. This might be due to the facile reduction of ring A and saturation of the alkene moiety in ring D. At this stage, we planned to complete the oxygenation at C(11) using manganic acetate as the oxidizing reagent. The alcohol **27** was then oxidized with PCC followed by treatment with $Mn(OAc)_3$ as described previously (cf. **18** → **20**). Unfortunately, the desired acetate **28** could not be detected. Most of the starting material was destroyed as the oxygenation proceeded. The negative results might be due to the instability of ring D and the steric crowding at C(11) (Scheme 8).

The fruitless acetoxylation at C(11) led us to change the oxygenation method to an enolate oxygenation and the saturated keto-alcohol **21** was selected as the starting material (Scheme 9). The C(1) oxygen functionality needed to be protected as a benzyl ether while an α-acetate group was required at C(7) for subsequent internal cyclization to form the D ring. Thus, benzylation of keto-alcohol **21** afforded the benzyl ether **29** in 85% yield. Desilylation of **29** with boron trifluoride in CH_2Cl_2 produced the alcohol **30** in 92% yield. Acetylation of **30** provided the acetate **16** in 94% yield. The acetate **16** was treated with LDA in THF at −78 °C to induce an intramolecular aldol cyclization. Indeed, the lactone **31** was isolated in 90% yield as a single diastereomer. Dehydration of **31** yielded the α,*β*-unsaturated lactone **32** in 94% yield. The constitution of **32** and especially the stereochemistry of the C(4α) methyl group and C(7*β*) proton were confirmed by an X-ray crystallographic analysis.[14] Catalytic hydrogenation of **32** over palladium caused debenzylation, saturation of the alkene moiety, and ring-opening of the epoxide functionality,[23] producing the crystalline diol **33** in 92% yield as a single compound. The ^1H NMR spectrum of **33** showed that the proton H(12) appeared at *δ* 4.0 ppm as a doublet. The coupling constant of 2.1 Hz was consistent with H(12) being in

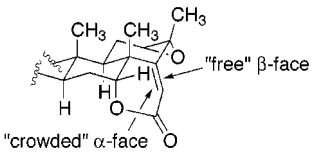
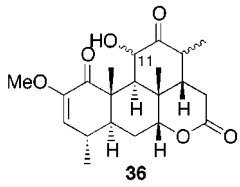


Figure 2.

the equatorial position (β-face) which supported our assignment of the stereochemistry of the C(12α) hydroxy group in **33**. The stereochemistry of the C(13) methyl group was not determined because it would be lost in the target molecule. The remarkable stereoselectivity for the saturation of the alkene moiety would be attributed to the more favorable attack of the hydrogen from the "free" β-face instead of the "crowded" α-face (Figure 2). Thus, the C(14) proton would be in the β-face. Swern oxidation of **33** followed by *O*-methylation furnished the α-methoxy enone **34** in excellent yield. With the α-methoxy enone **34** in hand, we decided to investigate the functionalization of ring C by using an enolate oxygenation. Toward this end, enolization of **34** with TMSOTf and Et_3N in CH_2Cl_2 at −10 °C yielded an enol silyl ether. The enol silyl ether was treated sequentially with *m*CPBA in the presence of $NaHCO_3$ in CH_2Cl_2 at −20 °C and TBAF giving rise to a 62% overall yield α-hydroxy ketone. Unfortunately, the thermodynamic product, C(13)-hydroxy ketone **35**, was obtained in stead of the desired kinetic product, C(11)-hydroxy ketone **36**.



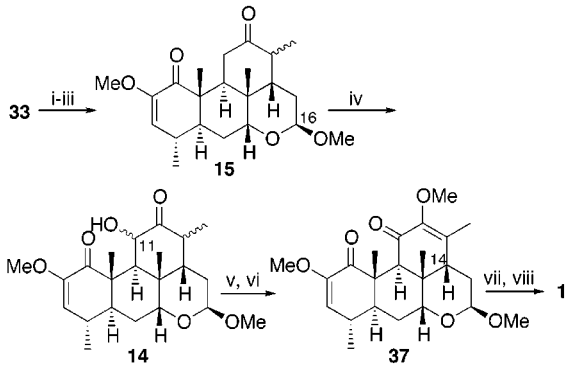
36

The disappointing results of the oxygenation of α-methoxy enone **34** led us to attempt an alternative enolate oxygenation. The MoO_5·pyridine·HMPA (MoOPH) complex had been demonstrated to be an efficient enolate oxygenation reagent.[9b,24] Thus, the use of MoOPH complex to complete our enolate oxygenation would be investigated.

The diol **33** was selected as the starting material. To our knowledge, the lactone carbonyl in **33** could not survive the conditions of enolization by LDA, thus, protection of the lactone carbonyl as a mixed acetal must be performed before the functionalization could be realized. The diol **33** was converted into ketone **15** via a series of chemical transformations (Scheme 10).

Reduction of the two carbonyl groups in **33** into an alcohol and a lactol with DIBAL-H in THF at −78 °C followed by acetalization of the lactol moiety with acidic methanol at 0 °C provided the mixed acetal. Swern oxidation of the mixed acetal followed by O-methylation

Scheme 10[a]



[a] Key: (i) DIBAL-H, THF, −78 °C then concentrated HCl (cat.), MeOH, 0 °C; (ii) DMSO, TFAA, CH_2Cl_2, −78 °C then Et_3N, −78 °C to rt; (iii) NaH, CH_3I, DMF, −20 °C [65% for steps from (i) to (iii)]; (iv) LDA, THF, −78 °C then MoOPH, −78 °C to 0 °C; (v) DMSO, TFAA, CH_2Cl_2, −78 °C then Et_3N, −78 °C to rt; (vi) NaH, CH_3I, DMF, −20 °C [53% for steps from (iv) to (vi)]; (vii) HOAc/H_2O (3:2, v/v), reflux; (viii) Ag_2CO_3/Celite, C_6H_6, reflux [79% for steps (vii) and (viii)].

furnished the ketone **15** in 65% overall yield. The ^1H NMR spectrum of **15** showed that the proton H(16) appeared at δ 4.69 ppm as a doublet. The small coupling constant of 3 Hz was consistent with H(16) being in the equatorial position ($J_{15\alpha,16\alpha} = J_{15\beta,16\alpha} = 3$ Hz) which supported our assignment of the stereochemistry of the C(16β) methoxy group in **15**.

With the ketone **15** in hand, we could investigate the enolate oxygenation to accomplish the functionalization of ring C. Thus, kinetic deprotonation of **15** with LDA in THF at −78 °C occurred at the C(11) methylene and subsequent treatment of the resulting enolate with MoOPH complex at −78 to 0 °C yielded successfully the corresponding α-hydroxy ketone **14** which underwent Swern oxidation and O-methylation in the manner as described previously (cf. **21** → **22**) to the desired bis(α-methoxy enone) **37** in moderate overall yield. At this stage, we accomplished the functionalization of ring A and ring C. The remaining task was to convert the mixed acetal into lactone and the total synthesis of (+)-quassin would be completed. Thus, selective hydrolysis of the acetal moiety in **37** with aqueous acetic acid under reflux followed by mild oxidation with Fetizon's reagent (Ag_2CO_3 on Celite)[25] in benzene under reflux afforded the target molecule, (+)-quassin (**1**), as a single product in 79% overall yield (Scheme 10). The synthetic (+)-quassin was identical to the purified commercial material purchased from Apin Chemicals Ltd (UK) by mp, $[\alpha]_D$, TLC, MS, IR, ^1H and ^{13}C NMR. The constitution of the synthetic (+)-quassin and especially the stereochemistry of the C(14β) proton were confirmed by an X-ray crystallographic analysis.[14]

Conclusion

The total synthesis of (+)-quassin from naturally occurring chiral (*S*)-(+)-carvone is realized. The tricyclic α-alcohol **3** is available in nine steps with 30.5% overall yield from the starting material,[13] and the target molecule has been constructed in a 19-step sequence from tricycle **3** with an 8.6% overall yield. Thus, (+)-quassin

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(24) (a) Vedejs, E.; Engler, D. A.; Telschow, J. E. *J. Org. Chem.* **1978**, *43*, 188. (b) Mimoun, M.; Seree de Roch, I.; Sajus, L. *Bull. Soc. Chim. Fr.* **1969**, 1481. (c) Vedejs, E. *J. Am. Chem. Soc.* **1974**, *96*, 5944. (d) Anderson, R. C.; Gunn, D. M. *J. Chem. Soc., Chem. Commun.* **1977**, 27.

(25) Fetizon, M.; Golfier, M. *C. R. Acad. Sci., Ser. C* **1968**, *267*, 900.

was harvested from (*S*)-(+)-carvone in 28 steps with an overall yield of about 2.6%. In comparison with Watt's synthesis,[12] in which 35 steps were required to obtain (+)-quassin from (*R*)-(−)-Wieland−Miescher ketone with an overall yield of less than 0.02%, our route was demonstrated to be a shorter, efficient, convergent, stereocontrolled, and enantiospecific synthesis.

In our synthesis, the synthetic strategy for the construction of tetracyclic carbon framework was based on a C → ABC → ABCD ring annulation sequence, and a separated functionalization of ring A and ring C was employed. Thus, the crucial points included (i) construction of the ABC ring system involving a stereoselective aldol reaction and an endo-selective intramolecular Diels−Alder reaction as the key steps, (ii) functionalization of ring A involving a regioselective allylic oxidation and a stereoselective acetoxylation as the crucial steps, (iii) stereocontrolled aldol cyclization of ring D, and (iv) an efficient kinetic controlled enolate oxygenation to functionalize ring C.

The established strategy can be applied to the syntheses of other tetracyclic members as well as pentacyclic quassinoids. Research in this direction is in progress.

Experimental Section

General Methods. Melting points are reported in degrees Celsius and are uncorrected. Optical rotations were measured at 589 nm. IR spectra were recorded on a FT-IR spectrometer as thin film on KBr disks. NMR spectra were measured at 250.13, 300.13, and 500.13 MHz (^{1}H) or at 62.89 and 75.47 MHz (^{13}C) in $CDCl_3$ solutions, unless stated otherwise. All chemical shifts were recorded in ppm relative to tetramethylsilane (δ = 0.0). Spin−spin coupling constants (J) were measured directly from the spectra. HRMS were performed at either the Shanghai Institute of Organic Chemistry, The Chinese Academy of Sciences, China, or the Department of Chemistry, The Chinese University of Hong Kong, Hong Kong. Carbon and hydrogen elemental analyses were carried out by the MEDAC Ltd, Department of Chemistry, Brunel University, Uxbridge, U.K. All reactions were monitored by TLC on aluminum precoated with silica gel $60F_{254}$ (E. Merck) and compounds were visualized with a spray of 5% w/v dodecamolybdophosphoric acid in EtOH and subsequent heating. E. Merck silica gel 60 (230−400 mesh) was used for flash chromatography. All solvents were reagent grade unless otherwise stated. Pyridine was distilled from BaO and stored in the presence of KOH pellets. MeOH was dried by Na and distilling from its sodium salt under N_2. Benzene, THF, and Et_2O were freshly distilled from Na/benzophenone ketyl under N_2. CH_2Cl_2 and CH_3CN were freshly distilled from CaH_2 under N_2. Diisopropylamine was freshly distilled from Na under N_2. DMF was dried over 4 Å molecular sieves. 2,6-Lutidine was dried by refluxing with BaO and distilling from it. MoOPH was prepared as described by Vedejs et al.[24a−b] Other reagents were purchased from commercial suppliers and were used without purification. All hexanes used are *n*-hexane.

7α-Acetoxy-12α,13α-epoxy-4,8*β*,13*β*-trimethyl-19-norpodocarp-3-ene-2,14-dione (9). To a solution of acetate **4** (173 mg, 0.52 mmol) in dry CH_3CN (15 mL) were added $Cr(CO)_6$ (115 mg, 0.52 mmol) and a 70% aqueous solution of TBHP (0.45 mL, 3.29 mmol). The reaction mixture was refluxed for 48 h under N_2. The reaction mixture was cooled to room temperature and was then diluted with Et_2O (20 mL). The mixture was filtered with a thin pad of silica gel, which was eluted with Et_2O. Concentration of the filtrate followed by flash column chromatography (3:2 Et_2O/hexane) afforded the enone **9** (110 mg) as a white solid and recovered 30 mg of the starting material (**4**) (74%, 83% conversion): R_f 0.21 (5:1 Et_2O/hexane); mp 179−180 °C; $[\alpha]_D$ = −55.3 (c = 1.2, $CHCl_3$); MS (EI) m/z 347 $[M + H]^+$; IR 1739 (ester C═O), 1711 (ketone C═O), 1661 cm^{-1} (enone C═O); ^{1}H NMR (500 MHz) δ 0.93 (3 H, s), 1.09 (3 H, s), 1.42 (3 H, s), 1.76 (1 H, d, J = 13 Hz), 1.89 (3 H, s), 1.97 (1 H, d, J = 13 Hz), 2.02 (3 H, s), 2.11 (1 H, d, J = 16 Hz), 2.19 (1 H, dt, J = 15, 3.5 Hz), 2.30 (1 H, m), 2.39 (1 H, dd, J = 13, 3.5 Hz), 2.61 (1 H, d, J = 16 Hz), 2.77 (1 H, bd, J = 14 Hz), 3.42 (1 H, brs), 5.41 (1 H, t, J = 3 Hz), 5.92 (1 H, s); ^{13}C NMR (62.89 MHz) δ 15.0, 16.3, 17.9, 20.6, 21.0, 21.9, 24.4, 36.4, 40.2, 42.7, 49.7, 52.7, 57.0, 59.2, 71.9, 127.1, 161.7, 169.8, 197.5, 203.2; HRMS calcd for $C_{20}H_{26}O_5$ 346.1780, found 346.1788.

12α,13α-Epoxy-14*β*-hydroxypicras-3-ene-2,16-dione (10). To a stirred solution of diisopropylamine (0.25 mL, 1.79 mmol) in dry THF (5 mL) was added a 1.6 M solution of *n*-butyllithium in *n*-hexane (1.1 mL, 1.76 mmol) at −78 °C under N_2. The reaction mixture was stirred for 10 min, and a solution of enone **9** (278 mg, 0.80 mmol) in dry THF (4 mL) was then added dropwise. The reaction mixture was stirred for 45 min at −78 °C and was then warmed to 0 °C. After 45 min at 0 °C, the reaction was quenched with saturated NH_4Cl (2 mL). The aqueous phase was extracted with CH_2Cl_2 (3 ×). The combined organic extracts were washed with brine, dried ($MgSO_4$), and filtered. Concentration of the filtrate followed by flash column chromatography (1:1 hexane/EtOAc) yielded the lactone **10** (263 mg, 95%) as a white solid: R_f 0.41 (4:1 EtOAc/hexane); mp 134−135 °C; $[\alpha]_D$ = +35.3 (c = 1.9, $CHCl_3$); MS (EI) m/z 346 $[M]^+$, 328; IR 3440 (OH), 1728 (lactone C═O), 1659 cm^{-1} (enone C═O); ^{1}H NMR (500 MHz) δ 0.99 (3 H, s), 1.10 (3 H, s), 1.38 (3 H, s), 1.52 (1 H, dd, J = 12.5, 5 Hz), 1.79−1.90 (2 H, m), 1.94 (3 H, s), 2.01 (1 H, d, J = 16 Hz), 2.10 (1 H, dd, J = 15.5, 5 Hz), 2.12 (1 H, brs), 2.28 (1 H, dt, J = 14.5, 3 Hz), 2.55 (1 H, d, J = 16 Hz), 2.64 (1 H, d, J = 19 Hz), 2.75 (1 H, bd, J = 14 Hz), 3.24 (1 H, brs), 3.31 (1 H, d, J = 19 Hz), 4.75 (1 H, t, J = 3 Hz), 5.92 (1 H, s); ^{13}C NMR (62.89 MHz) δ 14.0, 14.5, 19.0, 22.1, 22.4, 25.7, 37.5, 37.7, 38.9, 39.9, 42.0, 52.7, 60.6, 60.8, 74.0, 80.9, 127.0, 161.8, 170.5, 197.6, HRMS calcd for $C_{20}H_{26}O_5$ 346.1780, found 346.1788.

12α,13α-Epoxypicrasa-3,14-diene-2,16-dione (11). To a stirred solution of lactone **10** (139 mg, 0.40 mmol) in pyridine (15 mL) was added $SOCl_2$ (0.3 mL, 4.11 mmol) at 0 °C under N_2. The reaction mixture was stirred for 1 h and was then concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (40 mL), and the organic phase was washed with brine, dried ($MgSO_4$), and filtered. Concentration of the filtrate followed by flash column chromatography (1:1 hexane/EtOAc) provided the α,*β*-unsaturated lactone **11** (129 mg, 98%) as a white solid: R_f 0.40 (4:1 EtOAc/hexane); mp 165−166 °C; $[\alpha]_D$ = −22.1 (c = 1.4, $CHCl_3$); MS (EI) m/z 328 $[M]^+$; IR 1717 (conjugated lactone C═O), 1663 cm^{-1} (enone C═O); ^{1}H NMR (500 MHz) δ 0.96 (3 H, s), 1.20 (3 H, s), 1.57 (3 H, s), 1.69 (1 H, dd, J = 12 and 5 Hz), 1.83−1.94 (2 H, m), 1.96 (3 H, s), 2.02 (1 H, d, J = 15.5 Hz), 2.18 (1 H, dd, J = 15, 5 Hz), 2.36 (1 H, dt, J = 14.5, 3 Hz), 2.47 (1 H, d, J = 15.5 Hz), 2.82 (1 H, bd, J = 13.5 Hz), 3.31 (1 H, brs), 4.43 (1 H, t, J = 3 Hz), 5.93 (1 H, s), 6.18 (1 H, s); ^{13}C NMR (62.89 MHz) δ 13.9, 18.5, 20.0, 22.1, 25.2, 36.9, 39.5, 41.5, 42.4, 51.9, 56.3, 58.9, 78.4, 116.2, 127.2, 160.8, 163.9, 164.4, 197.0; HRMS calcd for $C_{20}H_{24}O_4$ 328.1674, found 328.1674.

12α-Hydroxypicrasa-3,13-diene-2,16-dione (12). To a stirred solution of α,*β*-unsaturated lactone **11** (25 mg, 0.076 mmol) and $NiCl_2 \cdot 6H_2O$ (2 mg) in MeOH (3 mL) at −35 °C was added $NaBH_4$ (12 mg, 0.32 mmol) in small batch over a period of 15 min. The reaction mixture was stirred for 1 h and was then quenched with saturated NH_4Cl (1 mL). The aqueous phase was extracted with CH_2Cl_2 (3 ×), and the combined organic extracts were washed with brine, dried ($MgSO_4$), and filtered. Concentration of the filtrate followed by flash column chromatography (1:1 hexane/EtOAc) yielded the alcohol **12** (15 mg, 60%) as a white solid: R_f 0.36 (4:1 EtOAc/hexane); mp 199−200 °C; $[\alpha]_D$ = +18.5 (c = 0.6, $CHCl_3$); MS (EI) m/z 330 $[M]^+$, 315; IR 3464 (OH), 1741 (lactone C═O), 1655 cm^{-1} (enone C═O); ^{1}H NMR (500 MHz) δ 0.88 (3 H, s), 1.07 (3 H, s), 1.58 (1 H, dd, J = 11 and 6.5 Hz), 1.78 (3 H, s), 1.79−1.82 (2 H, m), 1.91 (1 H, dd, J = 14.5, 3.5 Hz), 1.95 (3 H, s), 2.04 (1 H, d, J = 16 Hz), 2.13 (1 H, m), 2.38 (1 H, dt, J = 15, 3 Hz), 2.59 (1 H, d, J = 16 Hz), 2.81 (1 H, bd, J = 13.5 Hz), 3.13 (1 H, d, J = 15

Hz), 3.41 (1 H, d, J = 15 Hz), 4.27 (1 H, brs), 4.34 (1 H, t, J = 3 Hz), 5.93 (1 H, s); ^{13}C NMR (62.89 MHz) δ 13.1, 15.5, 19.6, 21.8, 24.7, 28.8, 32.8, 38.7, 39.8, 42.7, 43.2, 52.0, 68.0, 79.2, 127.4, 131.2, 133.2, 160.6, 171.2, 197.8; HRMS calcd for $C_{20}H_{26}O_4$ 330.1831, found 330.1834.

Picrasa-3,13-diene-2,12,16-trione (8). To a stirred solution of dry pyridine (0.23 mL, 2.85 mmol) and dry CH_2Cl_2 (9 mL) was added CrO_3 powder (138 mg, 1.38 mmol) at 0 °C under N_2. After 30 min at 0 °C, the reaction mixture was warmed to room temperature and was then stirred for another 30 min. To the reaction mixture was added a solution of alcohol **12** (23 mg, 0.070 mmol) in dry CH_2Cl_2 (1 mL). The reaction mixture was stirred for 2 h and was then diluted with dry Et_2O (20 mL). The mixture was filtered with a thin pad of silica gel that was eluted with Et_2O. Concentration of the filtrate followed by flash column chromatography (3:2 EtOAc/hexane) afforded the dienone **8** (19 mg, 83%) as a white solid: R_f 0.45 (4:1 EtOAc/hexane); mp 139−140 °C; $[\alpha]_D$ = +109.9 (c = 0.6, $CHCl_3$); MS (EI) m/z 328 $[M]^+$, 313; IR 1748 (lactone C=O), 1667 cm^{-1} (enone C=O); ^{1}H NMR (500 MHz) δ 0.98 (3 H, s), 1.22 (3 H, s), 1.81 (3 H, s), 1.97 (3 H, s), 2.02−2.05 (2 H, m), 2.21 (1 H, dd, J = 12, 4 Hz), 2.44−2.55 (4 H, m), 2.88 (1 H, bd, J = 13 Hz), 3.38 (1 H, d, J = 15 Hz), 3.63 (1 H, d, J = 15 Hz), 4.45 (1 H, brs), 5.95 (1 H, s); ^{13}C NMR (62.89 MHz) δ 11.3, 13.1, 19.8, 21.9, 24.6, 34.0, 34.2, 39.6, 39.8, 42.2, 46.5, 51.3, 79.0, 127.4, 131.4, 153.5, 160.2, 169.0, 197.0, 197.3, HRMS calcd for $C_{20}H_{24}O_4$ 328.1674, found 328.1678.

7α-(*tert*-Butyldimethylsiloxy)-12α,13α-epoxy-4,8*β*,13*β*-trimethyl-19-nopodocarp-3-en-14-one (19). To a solution of alcohol **3** (3.74 g, 12.9 mmol) in dry 2,6-lutidine (20 mL) was added TBSOTf (3 mL, 13.1 mmol) dropwise at room temperature under N_2. The reaction mixture was stirred for 5 days and was then diluted with CH_2Cl_2 (40 mL). The reaction mixture was washed with cold aqueous HCl (4 M, 2 ×), saturated Na_2CO_3, and brine. The organic phase was dried with $MgSO_4$ and filtered. Concentration of the filtrate followed by flash column chromatography (20:1 hexane/Et_2O) afforded the alkene **19** (3.85 g) as a white solid and recovered 0.93 g of the starting material **(3)** (98%, 75% conversion): R_f 0.71 (3:1 hexane/Et_2O); mp 75−76 °C; $[\alpha]_D$ = −73.6 (c = 3.1, $CHCl_3$); MS (EI) m/z 405 $[M + H]^+$; IR 1708 cm^{-1} (ketone C=O); ^{1}H NMR (500 MHz) δ 0.06 (3 H, s), 0.07 (3 H, s), 0.79 (3 H, s), 0.83 (9 H, s), 0.99 (3 H, s), 1.25 (1 H, dd, J = 21, 9 Hz), 1.36 (3 H, s), 1.54 (1 H, d, J = 14.5 Hz), 1.59 (3 H, s), 1.73 (1 H, m), 1.78 (1 H, dt, J = 14, 3.5 Hz), 1.86 (1 H, d, J = 14.5 Hz), 2.05 (2 H, brs), 2.32 (1 H, dd, J = 5.5, 3 Hz), 2.35 (1 H, dd, J = 7, 3 Hz), 2.63 (1 H, bd, J = 13 Hz), 3.34 (1 H, d, J = 2 Hz), 4.28 (1 H, d, J = 2 Hz), 5.29 (1 H, s); ^{13}C NMR (62.89 MHz) δ −5.5, −4.2, 13.1, 16.7, 18.0, 19.0, 20.2, 21.2, 22.7, 25.8, 27.3, 34.9, 35.1, 39.9, 52.6, 57.0, 59.6, 71.1, 77.2, 120.4, 134.4, 208.0; HRMS calcd for $C_{24}H_{40}O_3Si$ 404.2746, found 404.2736.

7α-(*tert*-Butyldimethylsiloxy)-12α,13α-epoxy-4,8*β*,13*β*-trimethyl-19-norpodocarp-3-ene-2,14-dione (18). This compound was prepared by treatment of alkene 1**9** (250 mg, 0.62 mmol) with $Cr(CO)_6$ (68 mg, 0.31 mmol) and a 70% aqueous solution of TBHP (0.34 mL, 2.49 mmol), as described above for the synthesis of **9**. Purification of the crude product by flash column chromatography (3:1 hexane/Et_2O then 40:1 CH_2Cl_2/Et_2O) provided the enone **18** (170 mg) as a white solid and recovered the starting material (**19**) (40 mg) (78%, 84% conversion): R_f 0.24 (1:1 Et_2O/hexane); mp 89−90 °C; $[\alpha]_D$ = −51.3 (c = 4.4, $CHCl_3$); MS (EI) m/z 419 $[M + H]^+$; IR 1708 (ketone C=O), 1668 cm^{-1} (enone C=O); ^{1}H NMR (500 MHz) δ 0.08 (3 H, s), 0.10 (3 H, s), 0.84 (9 H, s), 0.88 (3 H, s), 0.97 (3 H, s), 1.38 (3 H, s), 1.70 (1 H, m), 1.86 (1 H, d, J = 14.5 Hz), 1.89 (3 H, s), 1.93 (1 H, dt, J = 14 and 3 Hz), 2.08 (1 H, d, J = 16 Hz), 2.22 (1 H, dd, J = 14.5 and 3 Hz), 2.59 (1 H, d, J = 16 Hz), 2.61 (1 H, dd, J = 13 and 3.5 Hz), 3.08 (1 H, bd, J = 13 Hz), 3.37 (1 H, d, J = 2.5 Hz), 4.35 (1 H, brs), 5.91 (1 H, s); ^{13}C NMR (62.89 MHz) δ −5.5, −4.3, 15.1, 16.5, 17.9, 18.5, 20.1, 22.1, 25.7, 27.2, 35.0, 40.1, 42.0, 52.1, 52.9, 57.3, 59.3, 70.6, 126.7, 163.2, 198.5, 207.2; HRMS calcd for $C_{24}H_{38}O_4Si$ 418.2539, found 418.2556. Anal. Calcd for $C_{24}H_{38}O_4Si$: C, 68.86; H, 9.15. found: C, 68.56; H, 9.20.

1α-Acetoxy-7α-(*tert*-butyldimethylsiloxy)-12α,13α-epoxy-4,8*β*,13*β*-trimethyl-19-norpodocarp-3-ene-2,14-dione (20). To a solution of enone **18** (105 mg, 0.25 mmol) in dry benzene (15 mL) was added $Mn(OAc)_3$ (200 mg). After the reaction mixture had been refluxed for 1 h under N_2 using a Dean−Stark apparatus to separate the water of crystallization in $Mn(OAc)_3$, another portion of $Mn(OAc)_3$ (175 mg) was added, and the mixture was then refluxed for 16 h. The reaction mixture was cooled to room temperature and was then filtered with a pad of Celite which was washed with EtOAc. Concentration of the filtrate followed by flash column chromatography (3:1 hexane/Et_2O) afforded the acetate **20** (100 mg, 84%) as a white solid. Recrystallization from a mixture of EtOAc and hexane gave a single crystal which was analyzed by X-ray to confirm the structure, R_f 0.46 (2:1 Et_2O/hexane): mp 119−120 °C; $[\alpha]_D$ = +31.5 (c = 6.6, $CHCl_3$); MS (APCI) m/z 477 $[M + H]^+$; IR 1750 (ester C=O), 1707 (ketone C=O), 1676 cm^{-1} (enone C=O); ^{1}H NMR (500 MHz) δ 0.08 (3 H, s), 0.11 (3 H, s), 0.85 (9 H, s), 0.89 (3 H, s), 0.98 (3 H, s), 1.36 (3 H, s), 1.72 (1 H, t, J = 13.5 Hz), 1.81 (1 H, t, J = 13.5 Hz), 1.92 (3 H, s), 1.96 (1 H, dt, J = 13.5, 3.5 Hz), 2.08 (3 H, s), 2.27 (1 H, dt, J = 14.5, 3 Hz), 2.84 (1 H, dd, J = 13.5, 3 Hz), 3.33 (1 H, d, J = 3 Hz), 3.47 (1 H, bd, J = 13 Hz), 4.34 (1 H, d, J = 2.5 Hz), 5.15 (1 H, s), 5.91 (1 H, s); ^{13}C NMR (62.89 MHz) δ −5.6, −4.2, 14.0, 16.4, 17.8, 18.6, 19.9, 20.5, 22.4, 25.6, 26.7, 27.7, 35.9, 42.1, 52.0, 57.4, 59.1, 70.5, 74.2, 124.6, 164.6, 169.3, 192.7, 207.5; HRMS calcd for $C_{26}H_{41}O_6Si$ (M + H) 477.2672, found 477.2665.

7α-(*tert*-Butyldimethylsiloxy)-12α,13α-epoxy-1α-hydroxy-4,8*β*,13*β*-trimethyl-19-norpodocarp-3-ene-2,14-dione (17). To a solution of acetate **20** (110 mg, 0.23 mmol) in MeOH (8 mL) was added K_2CO_3 (160 mg, 1.16 mmol). The reaction mixture was stirred for 4 h at room temperature and was then concentrated in vacuo. The residue was diluted with Et_2O (20 mL) and acidified with 1 M aqueous HCl (2.4 mL). The aqueous phase was extracted with CH_2Cl_2 (3 ×). The combined organic extracts were washed with brine, dried ($MgSO_4$), and filtered. Concentration of the filtrate followed by flash column chromatography (2:1 hexane/Et_2O) yielded the alcohol **17** (87 mg, 87%) as a white solid: R_f 0.44 (2:1 Et_2O/hexane); mp 177−178 °C; $[\alpha]_D$ = −20.4 (c = 4.2, $CHCl_3$); MS (APCI) m/z 435 $[M + H]^+$; IR 3388 (OH), 1711 (ketone C=O), 1659 cm^{-1} (enone C=O); ^{1}H NMR (500 MHz) δ 0.08 (3 H, s), 0.10 (3 H, s), 0.80 (3 H, s), 0.85 (9 H, s), 0.99 (3 H, s), 1.38 (3 H, s), 1.57 (1 H, brs), 1.73 (1 H, t, J = 13.5 Hz), 1.84 (1 H, t, J = 13.5 Hz), 1.91 (3 H, s), 1.97 (1 H, dt, J = 13.5, 3.5 Hz), 2.23 (1 H, dt, J = 14.5, 3 Hz), 3.20 (1 H, dd, J = 13, 3.5 Hz), 3.37 (1 H, d, J = 2.5 Hz), 3.49 (1 H, bd, J = 11 Hz), 3.68 (1 H, s), 4.35 (1 H, d, J = 2.5 Hz), 5.88 (1 H, s); ^{13}C NMR (62.89 MHz) δ −5.5, −4.2, 14.5, 16.6, 17.9, 18.9, 19.6, 22.5, 25.6, 26.9, 27.5, 35.2, 42.4, 51.9, 57.2, 59.4, 70.5, 75.1, 124.0, 165.2, 198.2, 207.7; HRMS calcd for $C_{24}H_{39}O_5Si$ (M + H) 435.2566, found 435.2565.

7α-(*tert*-Butyldimethylsiloxy)-12α,13α-epoxy-1α-hydroxy-4α,8*β*,13*β*-trimethyl-19-norpodocarpane-2,14-dione (21). To a suspension of palladium on activated carbon (10%, 10 mg) in EtOH (2 mL), which had been stirred for 30 min under H_2 atmosphere at room temperature, was added a solution of alcohol **17** (67 mg, 0.15 mmol) in EtOH (8 mL). The reaction mixture was stirred for 4 h under H_2 and was then filtered. Concentration of the filtrate followed by flash column chromatography (2:1 hexane/Et_2O) provided the keto alcohol **21** (66.5 mg, 99%) as a white solid: R_f 0.55 (2:1 Et_2O/hexane); mp 166−167 °C; $[\alpha]_D$ = −65.1 (c = 4.4, $CHCl_3$); MS (APCI) m/z 437 $[M + H]^+$; IR 3520 (OH), 1702 cm^{-1} (ketone C=O); ^{1}H NMR (500 MHz) δ 0.06 (3 H, s), 0.09 (3 H, s), 0.71 (3 H, s), 0.87 (9 H, s), 0.95 (3 H, s), 0.96 (3 H, d, J = 8.5 Hz), 1.37 (3 H, s), 1.41 (1 H, d, J = 13 Hz), 1.58 (1 H, brs), 1.68 (1 H, m), 1.81 (1 H, d, J = 14 Hz), 1.84 (1 H, d, J = 14 Hz), 2.14 (1 H, dt, J = 14.5, 3.5 Hz), 2.24 (1 H, dd, J = 13.5, 4 Hz), 2.39 (1 H, ddd, J = 12, 3 Hz), 2.56 (1 H, dd, J = 14.5, 12.5 Hz), 3.13 (1 H, dd, J = 13, 3 Hz), 3.36 (1 H, d, J = 3 Hz), 3.66 (1 H, s), 4.27 (1 H, brs); ^{13}C NMR (62.89 MHz) δ −5.5, −4.0, 14.0, 16.6, 17.9, 18.7, 19.7, 19.9, 25.7, 27.3, 27.5, 32.2, 35.7, 42.4, 45.8, 52.6, 57.5, 59.5, 70.7, 78.0, 208.1, 212.0; HRMS calcd for $C_{24}H_{41}O_5Si$ (M

+ H) 437.2723, found 437.2727. Anal. Calcd for $C_{24}H_{40}O_5Si$: C, 66.02; H, 9.23. Found: C, 66.49; H, 9.50.

7α-(*tert*-Butyldimethylsiloxy)-12α,13α-epoxy-2-methoxy-4α,8*β*,13*β*-trimethyl-19-norpodocarp-2-ene-1,14-dione (22). To a stirred solution of DMSO (0.112 mL, 1.58 mmol) in dry CH_2Cl_2 (0.5 mL) was added TFAA (0.168 mL, 1.19 mmol) at −78 °C under N_2. After 15 min at −78 °C, to the mixture was added a solution of keto alcohol **21** (57.5 mg, 0.13 mmol) in dry CH_2Cl_2 (1 mL) dropwise. The reaction mixture was stirred for 40 min and then Et_3N (0.365 mL, 2.62 mmol) was added. After 5 min at −78 °C, the reaction mixture was allowed to warm to room temperature and was then stirred for 10 min. The reaction mixture was poured into H_2O (2 mL). The aqueous phase was extracted with CH_2Cl_2 (3 ×). The combined organic extracts were washed with brine, dried ($MgSO_4$), and filtered. Concentration of the filtrate followed by flash column chromatography (3:1 hexane/Et_2O) afforded **7α-(*tert*-butyldimethylsiloxy)-12α,13α-epoxy-2-hydroxy-4α,8*β*,13*β*-trimethyl-19-norpodocarp-2-ene-1,14-dione** (55.5 mg, 97%) as a colorless oil.

To a solution of **7α-(*tert*-butyldimethylsiloxy)-12α,13α-epoxy-2-hydroxy-4α,8*β*,13*β*-trimethyl-19-norpodocarp-2-ene-1,14-dione** (52 mg, 0.12 mmol) in DMF (1 mL) was added CH_3I (0.15 mL, 2.41 mmol). The reaction mixture was cooled to −20 °C and then NaH (60%, 48 mg, 1.20 mmol) was added. After 40 min at −20 °C under N_2, the reaction was quenched by slowly addition of MeOH (0.2 mL) followed by saturated NH_4Cl (2 mL). The aqueous phase was extracted with CH_2Cl_2 (3 ×). The combined organic extracts were washed with brine, dried ($MgSO_4$), and filtered. Concentration of the filtrate followed by flash column chromatography (3:1 hexane/Et_2O) yielded the α-methoxy enone **22** (52 mg, 97%) as a white solid.

Data for **7α-(*tert*-butyldimethylsiloxy)-12α,13α-epoxy-2-hydroxy-4α,8*β*,13*β*-trimethyl-19-norpodocarp-2-ene-1,14-dione**: R_f 0.64 (2:1 Et_2O/hexane); $[\alpha]_D$ = −51.4 (c = 3.2, $CHCl_3$); MS (APCI) m/z 435 $[M + H]^+$; IR 3443 (OH), 1710, (ketone C═O), 1681 cm^{-1} (enone C═O); ^1H NMR (500 MHz) δ 0.05 (3 H, s), 0.07 (3 H, s), 0.80 (9H, s), 0.98 (3 H, s), 1.07 (3 H, d, J = 7 Hz), 1.21 (3 H, s), 1.37 (3 H, s), 1.56 (1 H, t, J = 13.5 Hz), 1.79 (1 H, dt, J = 14, 3.5 Hz), 1.92 (1 H, dd, J = 14.5, 13 Hz), 2.15 (1 H, dddd, J = 13, 9.5, 2.5 Hz), 2.37 (1 H, m), 2.91 (1 H, dd, J = 13, 3.5 Hz), 3.36 (1 H, d, J = 3.5 Hz), 3.42 (1 H, dt, J = 15, 3.5 Hz), 4.24 (1 H, d, J = 3 Hz), 5.77 (1 H, d, J = 2.5 Hz), 5.87 (1 H, brs); ^{13}C NMR (62.89 MHz) δ −5.4, −4.2, 13.9, 15.0, 16.5, 17.9, 19.2, 22.4, 25.8, 27.1, 29.3, 30.9, 43.2, 45.1, 52.4, 57.1, 59.6, 70.0, 120.8, 142.8, 201.3, 207.5.

Data for **22**: R_f 0.26 (1:1 Et_2O/hexane); mp 158−159 °C; $[\alpha]_D$ = −43.8 (c = 3.0, $CHCl_3$); MS (APCI) m/z 449 $[M + H]^+$; IR 1705 (ketone C═O), 1692 (enone C═O), 1628 cm^{-1} (C═C); ^1H NMR (500 MHz) δ 0.05 (6 H, s), 0.80 (9 H, s), 0.95 (3 H, s), 1.08 (3 H, d, J = 7 Hz), 1.21 (3 H, s), 1.36 (3 H, s), 1.53 (1 H, d, J = 11 Hz), 1.78 (1 H, bd, J = 14 Hz), 1.83 (1 H, d, J = 13 Hz), 2.08 (1 H, m), 2.35 (1 H, m), 2.95 (1 H, dd, J = 12.5, 3.5 Hz), 3.21 (1 H, bd, J = 13 Hz), 3.35 (1 H, d, J = 3 Hz), 3.58 (3 H, s), 4.24 (1 H, d, J = 3 Hz), 5.34 (1 H, d, J = 2 Hz); ^{13}C NMR (62.89 MHz) δ −5.5, −4.2, 13.5, 16.5, 17.9, 19.2, 19.6, 22.2, 25.7, 27.3, 28.8, 31.3, 42.7, 46.2, 52.2, 54.8, 56.9, 59.7, 70.0, 117.5, 147.5, 199.5, 207.8; HRMS calcd for $C_{25}H_{41}O_5Si$ (M + H) 449.2723, found 449.2718.

12α,13α-Epoxy-7α-hydroxy-2-methoxy-4α,8*β*,13*β*-trimethyl-19-norpodocarp-2-ene-1,14-dione (23). To a solution of α-methoxy enone **22** (41.5 mg, 0.093 mmol) in dry THF (5 mL) was added a 1.0 M solution of TBAF in THF (0.28 mL, 0.28 mmol). The reaction mixture was warmed to 50 °C and was then stirred for 48 h at about 50 °C under N_2. The reaction mixture was cooled to room temperature and was then poured into saturated $NaHCO_3$ (2 mL). The aqueous phase was extracted with CH_2Cl_2 (3 ×). The combined organic extracts were washed with brine, dried ($MgSO_4$), and filtered. Concentration of the filtrate followed by flash column chromatography (1:1 hexane/Et_2O) yielded the alcohol **23** (26.5 mg) as a white solid and recovered the starting material (**22**) (4 mg) (95%, 90% conversion): R_f 0.33 (4:1 Et_2O/hexane); mp 110−111 °C; $[\alpha]_D$ = −34.3 (c = 2.1, $CHCl_3$); MS (EI) m/z 334 $[M]^+$; IR 3511 (OH), 1697 (C═O), 1634 cm^{-1} (C═C); ^1H NMR (500 MHz) δ 1.04 (3 H, s), 1.13 (3 H, d, J = 7 Hz), 1.23 (3 H, s), 1.43 (3 H, s), 1.55 (1 H, d, J = 13.5 Hz), 1.90 (1 H, d, J = 14 Hz), 1.96 (1 H, dt, J = 14.5, 3.5 Hz), 2.06 (1 H, dddd, J = 13, 10, 3 Hz), 2.33 (1 H, m), 2.60 (1 H, brs), 2.64 (1 H, dd, J = 12.5, 3.5 Hz), 3.25 (1 H, dt, J = 15, 3 Hz), 3.39 (1 H, d, J = 1.5 Hz), 3.57 (3 H, s), 4.16 (1 H, brs), 5.36 (1 H, d, J = 2 Hz); ^{13}C NMR (62.89 MHz) δ 13.3, 16.0, 17.5, 19.6, 22.6, 25.9, 28.8, 31.5, 41.8, 46.4, 51.3, 54.9, 56.1, 59.7, 68.6, 117.8, 147.5, 199.1, 209.1; HRMS calcd for $C_{19}H_{26}O_5$ 334.1780, found 334.1783.

7α-Acetoxy-12α,13α-epoxy-2-methoxy-4α,8*β*,13*β*-trimethyl-19-norpodocarp-2-ene-1,14-dione (24). To a solution of alcohol **23** (19 mg, 0.057 mmol) and DMAP (68 mg, 0.56 mmol) in dry CH_2Cl_2 (2 mL) was added Ac_2O (26 μL, 0.28 mmol). The reaction mixture was stirred for 48 h at room temperature and was then poured into saturated NH_4Cl (2 mL). The aqueous phase was extracted with CH_2Cl_2 (3 ×). The combined organic extracts were washed with brine, dried ($MgSO_4$), and filtered. Concentration of the filtrate followed by flash column chromatography (25:1 CH_2Cl_2/Et_2O) provided the acetate **24** (19 mg, 89%) as a white solid: R_f 0.29 (4:1 Et_2O/hexane); mp 185−186 °C; $[\alpha]_D$ = −62.6 (c = 2.6, $CHCl_3$); MS (EI) m/z 376 $[M]^+$; IR 1731 (ester C═O), 1710 (ketone C═O), 1680 (enone C═O), 1634 cm^{-1} (C═C); ^1H NMR (500 MHz) δ 1.05 (3 H, d, J = 6.5 Hz), 1.07 (3 H, s), 1.25 (3 H, s), 1.40 (3 H, s), 1.55 (1 H, d, J = 13 Hz), 1.79 (1 H, dddd, J = 13, 9.5, 3 Hz), 1.91 (1 H, t, J = 13.5 Hz), 1.97 (3 H, s), 2.06 (1 H, dt, J = 14.5, 3.5 Hz), 2.35 (1 H, m), 2.74 (1 H, dd, J = 12.5, 3 Hz), 3.25 (1 H, dt, J = 15, 3 Hz), 3.39 (1 H, d, J = 2.5 Hz), 3.58 (3 H, s), 5.28 (1 H, d, J = 2 Hz), 5.36 (1 H, d, J = 2 Hz); ^{13}C NMR (62.89 MHz) δ 13.5, 16.3, 18.3, 19.6, 21.0, 22.6, 24.2, 29.9, 31.3, 43.3, 46.2, 49.5, 55.0, 56.5, 59.5, 71.2, 117.5, 147.6, 170.0, 199.0, 205.1; HRMS calcd for $C_{21}H_{28}O_6$ 376.1886, found 376.1880.

12α,13α-Epoxy-14*β*-hydroxy-2-methoxypicras-2-ene-1,16-dione (25). To a stirred solution of diisopropylamine (54 μL, 0.39 mmol) in dry THF (0.5 mL) was added a 2.5 M solution of *n*-butyllithium in *n*-hexane (154 μL, 0.39 mmol) at −78 °C under N_2. The reaction mixture was stirred for 15 min and a solution of acetate **24** (66 mg, 0.18 mmol) in dry THF (6 mL) was then added dropwise. After 30 min at −78 °C, the reaction was quenched with saturated NH_4Cl (2 mL). The aqueous phase was extracted with CH_2Cl_2 (3 ×). The combined organic extracts were washed with brine, dried ($MgSO_4$), and filtered. Concentration of the filtrate followed by flash column chromatography (20:1 then 2:1 CH_2Cl_2/Et_2O) afforded the lactone **25** (35 mg) as a white solid and recovered the starting material (**24**) (18 mg) (73%, 73% conversion): R_f 0.26 (2:1 EtOAc/hexane); mp 220 °C dec; $[\alpha]_D$ = +46.6 (c = 2.3, $CHCl_3$); MS (EI) m/z 376 $[M]^+$; IR 3478 (OH), 1722 (lactone C═O), 1695 (enone C═O), 1633 cm^{-1} (C═C); ^1H NMR (500 MHz) δ 1.07 (3 H, s), 1.14 (3 H, d, J = 7 Hz), 1.26 (3 H, s), 1.36 (3 H, s), 1.66 (1 H, d, J = 12.5 Hz), 1.80−1.86 (3 H, m), 1.91 (1 H, dd, J = 12, 4 Hz), 2.08 (1 H, dt, J = 14.5, 3.5 Hz), 2.38 (1 H, m), 2.60 (1 H, d, J = 19 Hz), 2.95 (1 H, bd, J = 14 Hz), 3.20 (1 H, brs), 3.38 (1 H, d, J = 19 Hz), 3.57 (3 H, s), 4.63 (1 H, brs), 5.38 (1 H, d, J = 2.5 Hz); ^{13}C NMR (62.89 MHz) δ 13.2, 15.3, 19.0, 19.6, 24.5, 25.5, 31.3, 32.0, 37.4, 37.5, 41.9, 46.0, 55.0, 60.1, 61.2, 74.1, 79.9, 118.0, 147.6, 171.1, 199.0; HRMS calcd for $C_{21}H_{28}O_6$ 376.1886, found 376.1899.

12α,13α-Epoxy-2-methoxypicrasa-2,14-diene-1,16-dione (26). Following the same procedure used to prepare **11** from **10**, the lactone **25** (35 mg, 0.093 mmol) was converted to the α,*β*-unsaturated lactone **26** (31.5 mg, 95%) as a white solid: R_f 0.25 (2:1 EtOAc/hexane); mp 198 °C dec; $[\alpha]_D$ = −30.3 (c = 2.0, $CHCl_3$); MS (EI) m/z 358 $[M]^+$; IR 1715 (conjugated lactone C═O), 1692 (enone C═O), 1641 cm^{-1} (C═C); ^1H NMR (500 MHz) δ 1.17 (3 H, d, J = 7 Hz), 1.19 (6 H, s), 1.55 (3 H, s), 1.79 (1 H, m), 1.87−1.93 (2 H, m), 1.97 (1 H, dd, J = 12, 4.5 Hz), 2.17 (1 H, dt, J = 14.5, 3 Hz), 2.37 (1 H, m), 3.19 (1 H, dd, J = 15, 4 Hz), 3.26 (1 H, d, J = 2 Hz), 3.56 (3 H, s), 4.28 (1 H, t, J = 2.5 Hz), 5.39 (1 H, d, J = 2.5 Hz), 6.15 (1 H, s); ^{13}C NMR (62.89 MHz) δ 12.5, 14.9, 18.7, 19.8, 24.0, 25.3, 31.6, 35.5, 36.8, 42.2, 45.5, 54.9, 55.8, 59.5, 77.9, 116.2, 117.8, 147.6, 164.3, 165.1, 198.2; HRMS calcd for $C_{21}H_{26}O_5$ 358.1780, found 358.1777.

12α-Hydroxy-2-methoxypicrasa-2,13-diene-1,16-dione (27). Following the same procedure used to prepare **12** from **11**, the α,β-unsaturated lactone **26** (30 mg, 0.084 mmol) was converted into the alcohol **27** (9 mg, 30%) as a white solid: R_f 0.32 (3:1 EtOAc/hexane); mp 201−202 °C; ^{1}H NMR (250 MHz) δ 1.09 (3 H,s), 1.14 (3 H, d, J = 6.9 Hz), 1.17 (3 H, s), 1.72 (2 H, brs), 1.78 (3 H, s), 1.84 (1 H, d, J = 7 Hz), 2.05 (1 H, dd, J = 13, 2 Hz), 2.15 (1 H, dd, J = 14, 5.8 Hz), 2.23 (1 H, d, J = 6 Hz), 2.35 (1 H, m), 2.65 (1 H, bd, J = 14 Hz), 3.08 (1 H, bd, J = 15 Hz), 3.38 (1 H, d, J = 15 Hz), 3.57 (3 H, s), 4.09 (1 H, brs), 4.23 (1 H, brs), 5.36 (1 H, d, J = 2.5 Hz); ^{13}C NMR (62.89 MHz) δ 11.6, 15.7, 19.6, 24.7, 29.7, 30.7, 31.6, 32.7, 36.9, 38.7, 43.0, 45.5, 55.0, 68.8, 78.7, 117.4, 132.2, 132.4, 147.8, 171.8, 199.9.

1α-Benzyloxy-7α-(*tert*-butyldimethylsiloxy)-12α,13α-epoxy-4α,8β,13β-trimethyl-19-norpodocarpane-2,14-dione (29). To a stirred solution of keto alcohol **21** (20 mg, 0.046 mmol) in dry THF (5 mL) was added NaH (60%, 18 mg, 0.45 mmol) at 0 °C under N_2. After 1 h at 0 °C, the reaction mixture was added BnBr (0.11 mL, 0.93 mmol) and a catalytic amount of tetra-*n*-butylammonium iodide (TBAI). The reaction mixture was allowed to warm to room temperature and was then stirred for 8 h. The reaction was quenched by slowly addition of MeOH (0.2 mL) followed by saturated NH_4Cl (2 mL). The aqueous phase was extracted with CH_2Cl_2 (3 ×). The combined organic extracts were washed with brine, dried ($MgSO_4$), and filtered. Concentration of the filtrate followed by flash column chromatography (9:1 hexane/EtOAc) afforded the ketone **29** (20.5 mg, 85%) as a white solid: R_f 0.61 (1:1 Et_2O/hexane); mp 121−122 °C; $[\alpha]_D$ = −65.2 (c = 1.0, $CHCl_3$); MS (EI) m/z 527 $[M + H]^+$; IR 1709 cm^{-1} (ketone C═O); ^{1}H NMR (300 MHz) δ 0.06 (3 H, s), 0.07 (3 H, s), 0.68 (3 H, s), 0.83 (9 H, s), 0.92 (3 H, s), 0.93 (3 H, d, J = 6 Hz), 1.37 (3 H, s), 1.64−1.74 (4 H, m), 1.78 (1 H, dt, J = 11, 3 Hz), 2.25 (1 H, dd, J = 13.8, 4.2 Hz), 2.47 (1 H, d, J = 12.6 Hz), 2.51 (1 H, d, J = 12.6 Hz), 3.23 (1 H, brs), 3.29 (1 H, brs), 3.35 (1 H, dd, J = 11.4, 4.2 Hz), 4.26 (1 H, brs), 4.30 (1 H, d, J = 12 Hz), 4.49 (1 H, d, J = 12 Hz), 7.25−7.40 (5 H, m); ^{13}C NMR (62.89 MHz) δ −5.5, −3.9, 14.0, 16.7, 18.0, 18.9, 19.7, 19.9, 25.7, 27.6, 32.4, 36.7, 42.8, 46.7, 52.7, 57.2, 59.5, 70.7, 71.4, 84.5, 127.7, 128.1, 128.3, 137.2, 208.4, 211.9; HRMS calcd for $C_{31}H_{47}O_5Si$ (M + H) 527.3192, found 527.3173.

1α-Benzyloxy-12α,13α-epoxy-7α-hydroxy-4α,8β,13β-trimethyl-19-norpodocarpane-2,14-dione (30). To a solution of ketone **29** (53 mg, 0.10 mmol) in dry CH_2Cl_2 (8 mL) was added $Et_2O{\cdot}BF_3$ (63 μL, 0.50 mmol) at 0 °C under N_2. The reaction mixture was allowed to warm to about 10 °C and was then stirred for 6 h. The reaction was quenched with saturated NH_4Cl (2 mL), and the aqueous phase was extracted with CH_2Cl_2 (3×). The combined organic extracts were washed with brine, dried ($MgSO_4$), and filtered. Concentration of the filtrate followed by flash column chromatography (7:1 hexane/EtOAc) yielded the alcohol **30** (38 mg, 92%) as a white solid: R_f 0.31 (1:1 Et_2O/hexane); mp 143−144 °C; $[\alpha]_D$ = −36.5 (c = 2.1, $CHCl_3$); MS (EI) m/z 413 $[M + H]^+$; IR 3563 (OH), 1703 cm^{-1} (ketone C═O); ^{1}H NMR (300 MHz) δ 0.68 (3 H, s), 0.96 (3 H, s), 1.00 (3 H, d, J = 6.6 Hz), 1.42 (3 H, s), 1.43−1.53 (2 H, m), 1.61 (1 H, d, J = 13.5 Hz), 1.70 (1 H, m), 1.97 (1 H, dt, J = 14.4, 3 Hz), 1.99 (1 H, brs), 2.23 (1 H, dd, J = 13.5, 3.9 Hz), 2.33 (1 H, m), 2.55 (1 H, t, J = 13 Hz), 2.91 (1 H, dd, J = 12.6, 4.2 Hz), 3.20 (2 H, brs), 4.16 (1 H, d, J = 12 Hz), 4.17 (1 H, brs), 4.61 (1 H, d, J = 12 Hz), 7.30−7.37 (5 H, m); ^{1}H NMR (300 MHz, $CDCl_3$ + D_2O) δ 0.68 (3 H, s), 0.96 (3 H, s), 1.00 (3 H, d, J = 6.3 Hz), 1.42 (3 H, s), 1.40−1.53 (2 H, m), 1.61 (1 H, d, J = 13.2 Hz), 1.71 (1 H, m), 1.97 (1 H, dt, J = 14.1, 3 Hz), 2.23 (1 H, dd, J = 13.8, 4.2 Hz), 2.33 (1 H, m), 2.55 (1 H, t, J = 13 Hz), 2.90 (1 H, dd, J = 12.3, 3.9 Hz), 3.20 (2 H, brs), 4.16 (1 H, d, J = 12 Hz), 4.17 (1 H, brs), 4.61 (1 H, d, J = 12.3 Hz), 7.28−7.37 (5 H, m); ^{13}C NMR (62.89 MHz) δ 13.3, 16.2, 17.3, 19.7, 19.9, 26.3, 27.5, 32.7, 36.5, 43.0, 46.4, 51.7, 56.1, 59.3, 69.3, 70.8, 83.1, 128.0, 128.4, 128.9, 136.7, 209.3, 211.7; HRMS calcd for $C_{25}H_{33}O_5$ (M + H) 413.2328, found 413.2321.

7α-Acetoxy-1α-benzyloxy-12α,13α-epoxy-4α,8β,13β-trimethyl-19-norpodocarpane-2,14-dione (16). Following the same acetylation procedure used in the preparation of **24** from **23**, the alcohol **30** (30 mg, 0.073 mmol) was converted into the acetate **16** (31 mg, 94%) as a white solid: R_f 0.64 (2:1 Et_2O/hexane); mp 173−174 °C; $[\alpha]_D$ = −66.0 (c = 1.5, $CHCl_3$); MS (EI) m/z 455 $[M + H]^+$; IR 1744 (ester C═O), 1706 cm^{-1} (ketone C═O); ^{1}H NMR (300 MHz) δ 0.70 (3 H, s), 0.92 (3 H, d, J = 6.6 Hz), 1.01 (3 H, s), 1.40 (3 H, s), 1.44 (1 H, d, J = 14.7 Hz), 1.62−1.73 (3 H, m), 2.03 (3 H, s), 2.07 (1 H, m), 2.15 (1 H, bd, J = 10.8 Hz), 2.25 (1 H, dd, J = 13.8, 4.2 Hz), 2.50 (1 H, t, J = 13 Hz), 3.03 (1 H, dd, J = 11.4, 4.8 Hz), 3.22 (1 H, brs), 3.27 (1 H, brs), 4.25 (1 H, d, J = 12 Hz), 4.59 (1 H, d, J = 11.7 Hz), 5.30 (1 H, brs), 7.30−7.42 (5 H, m); ^{13}C NMR (62.89 MHz) δ 13.7, 16.4, 18.0, 19.7, 19.9, 21.1, 24.5, 28.6, 32.3, 37.6, 42.7, 46.3, 49.9, 56.5, 59.2, 71.0, 71.9, 83.3, 128.0, 128.4, 128.5, 136.8, 170.1, 205.7, 211.1; HRMS calcd for $C_{27}H_{35}O_6$ (M + H) 455.2433, found 455.2446.

1α-Benzyloxy-12α,13α-epoxy-14β-hydroxypicrasane-2,16-dione (31). Following the same cyclization procedure used to prepare **25** from **24**, the acetate **16** (24 mg, 0.053 mmol) was converted into the lactone **31** (21.5 mg, 90%) as a white solid: R_f 0.21 (2:1 Et_2O/hexane); mp 187−188 °C; $[\alpha]_D$ = +10.8 (c = 1.6, $CHCl_3$); MS (EI) m/z 455 $[M]^+$; IR 3418 (OH), 1714 cm^{-1} (C═O); ^{1}H NMR (300 MHz) δ 0.74 (3 H, s), 1.00 (3H, d, J = 5.4 Hz), 1.01 (3H, s), 1.36 (3H, s), 1.43 (1 H, d, J = 5.7 Hz), 1.52 (1 H, d, J = 15 Hz), 1.61 (1H, m), 1.68−1.83 (2H, m), 2.02−2.17 (2H, m), 2.21 (1H, d, J = 4.8 Hz), 2.26 (1H, t, J = 3.3 Hz), 2.51 (1H, t, J = 13 Hz), 2.68 (1H, d, J = 18.6 Hz), 3.07 (1H, brs), 3.15 (1H, brs), 3.34 (1H, d, J = 18.9 Hz), 4.15 (1H, d, J = 12 Hz), 4.56 (1H, d, J = 12 Hz), 4.62 (1H, t, J = 3 Hz), 7.28−7.39 (5H, m); ^{1}H NMR (300 MHz, $CDCl_3$ + D_2O) δ 0.74 (3H, s), 1.00 (3H, d, J = 5.1 Hz), 1.01 (3H, s), 1.36 (3H, s), 1.43 (1H, d, J = 5.7 Hz), 1.52 (1H, d, J = 15 Hz), 1.61 (1H, m), 1.68−1.80 (1H, m), 2.02−2.17 (2H, m), 2.21 (1H, d, J = 4.5 Hz), 2.26 (1H, t, J = 3.3 Hz), 2.51 (1H, t, J = 13 Hz), 2.68 (1H, d, J = 18.6 Hz), 3.07 (1H, brs), 3.15 (1H, brs), 3.34 (1H, d, J = 18.6 Hz), 4.15 (1H, d, J = 12 Hz), 4.56 (1H, d, J = 12 Hz), 4.63 (1H, t, J = 3 Hz), 7.29−7.39 (5H, m); ^{13}C NMR (62.89 MHz) δ 13.0, 14.3, 19.0, 19.9, 21.5, 25.9, 30.2, 32.6, 36.6, 37.5, 37.6, 42.6, 46.0, 60.4, 60.5, 71.1, 74.1, 81.2, 83.2, 128.1, 128.5, 136.5, 171.7, 211.4; HRMS calcd for $C_{27}H_{35}O_6$ (M + H) 455.2433, found 455.2443.

1α-Benzyloxy-12α,13α-epoxypicras-14-ene-2,16-dione (32). Following the same dehydration procedure used in the preparation of **11**, the lactone **31** (15 mg, 0.033 mmol) was converted to the α,β-unsaturated lactone **32** (13.5 mg, 94%) as a white solid. Recrystallization from a mixture of Et_2O and CH_2Cl_2 gave a single crystal which was analyzed by X-ray to prove the structure: R_f 0.24 (2:1 Et_2O/hexane); mp 193−194 °C; $[\alpha]_D$ = −82.8 (c = 1.1, $CHCl_3$); MS (EI) m/z 437 $[M + H]^+$; IR 1714 cm^{-1} (C═O); ^{1}H NMR (300 MHz) δ 0.70 (3H, s), 1.04 (3H, d, J = 6.6 Hz), 1.10 (3H, s), 1.42 (1H, dd, J = 15.3 and 5.7 Hz), 1.53 (3H, s), 1.65−1.77 (3H, m), 2.12−2.28 (4H, m), 2.57 (1H, *t*, J = 13 Hz), 3.10 (2H, brs), 4.12 (1H, d, J = ^{1}2.3 Hz), 4.29 (1H, t, J = 3 Hz), 4.55 (1H, d, J = 12 Hz), 6.18 (1H, s), 7.25−7.38 (5H, m); ^{13}C NMR (62.89 MHz) δ 12.2, 18.5, 20.0, 21.0, 25.8, 33.3, 36.9, 37.3, 42.3, 45.8, 55.8, 58.8, 70.9, 78.4, 82.8, 116.1, 128.1, 128.5, 128.9, 136.2, 164.7, 211.4; HRMS calcd for $C_{27}H_{33}O_5$ (M + H) 437.2328, found 437.2320.

1α,12α-Dihydroxypicrasane-2,16-dione (33). To a suspension of palladium on activated carbon (10%, 2 mg) in EtOH (1 mL), which had been stirred for 30 min under H_2 atmosphere at room temperature, was added a solution of α,β-unsaturated lactone **32** (15 mg, 0.034 mmol) in EtOH (5 mL). The reaction mixture was stirred for 2 days under H_2 and was then filtered. Concentration of the filtrate followed by flash column chromatography (2:1 Et_2O/CH_2Cl_2) provided the alcohol **33** (11 mg, 92%) as a white solid: R_f 0.16 (4:1 Et_2O/hexane); mp 215 °C dec; $[\alpha]_D$ = +23.3 (c = 0.5, $CHCl_3$); MS (EI) m/z 350 $[M]^+$; IR 3390 (OH), 1722 (lactone C═O), 1714 cm^{-1} (ketone C═O); ^{1}H NMR (300 MHz) δ 0.66 (3H, s), 0.98 (3H, d, J = 6.3 Hz), 1.01 (3H, d, J = 7.2 Hz), 1.11 (3H, s), 1.60−1.80 (6H, m), 1.92−1.97 (1H, m), 2.12 (1H, bd, J = 12.6 Hz), 2.19 (1H, dd, J = 14, 4 Hz), 2.42 (1H, dd, J = 11.7, 3.9 Hz), 2.51 (1H, dd, J = 19.5, 6.6 Hz), 2.58 (1H, dd, J = 13.8, 12.6 Hz), 3.37 (1H, dd, J = 19.2, 12.3 Hz), 3.49 (2H, brs), 3.60 (1H, s), 4.01 (1H, d, J = 2.1 Hz), 4.20 (1H, brs); ^{1}H NMR (300 MHz,

$CDCl_3$ + D_2O) δ 0.66 (3H, s), 0.98 (3H, d, J = 6.3 Hz), 1.01 (3H, d, J = 7.2 Hz), 1.11 (3H, s), 1.60−1.80 (6H, m), 1.92−1.97 (1H, m), 2.12 (1H, bd, J = 12.9 Hz), 2.19 (1H, dd, J = 14.5, 3.8 Hz), 2.41 (1H, dd, J = 12.3, 3.9 Hz), 2.51 (1H, dd, J = 19.5, 6.9 Hz), 2.58 (1H, dd, J = 13.8, 12.6 Hz), 3.37 (1H, dd, J = 19.5, 12.3 Hz), 3.59 (1H, s), 4.00 (1H, d, J = 2.1 Hz), 4.20 (1H, brs); ^{13}C NMR (62.89 MHz) δ 12.7, 14.7, 19.8, 21.3, 26.3, 27.3, 27.7, 29.3, 29.7, 32.2, 32.3, 35.2, 36.4, 42.2, 45.4, 45.6, 71.3, 83.6, 172.9, 212.0; HRMS calcd for $C_{20}H_{31}O_5$ (M + H) 351.2171, found 351.2165.

2-Methoxypicras-2-ene-1,12,16-trione (34). Following the same procedure used to prepare **22** from **21**, the alcohol **33** (7 mg, 0.02 mmol) was converted into **2-hydroxypicras-2-ene-1,12,16-trione** (6.5 mg, 94%) as a white solid, and **2-hydroxypicras-2-ene-1,12,16-trione** (6 mg, 0.017 mmol) was then converted into the α-methoxy enone **34** (5.8 mg, 94%) as a white solid.

Data of **2-hydroxypicras-2-ene-1,12,16-trione**: R_f 0.44 (4:1 EtOAc/hexane); ^{1}H NMR (250 MHz) δ 1.00 (3H, d, J = 6.8 Hz), 1.12 (3H, d, J = 7 Hz), 1.24 (3H, s), 1.45 (3H, s), 1.87 (1H, brs), 1.91 (1H, brs), 1.95−2.24 (5H, m), 2.41−2.52 (2H, m), 2.62 (1H, dd, J = 16.7, 4.3 Hz), 2.88 (1H, m), 3.56 (1H, dd, J = 14, 3 Hz), 4.35 (1H, brs), 5.79 (1H, d, J = 2.4 Hz).

Data of **34**: R_f 0.40 (4:1 EtOAc/hexane); mp 210 °C dec; $[\alpha]_D$ = +14.0 (c = 0.4, $CHCl_3$); MS (EI) m/z 360 $[M]^+$; IR 1728 (lactone C═O), 1714 (ketone C═O), 1694 (enone C═O), 1634 cm^{-1} (C═C); ^{1}H NMR (300 MHz) δ 0.98 (3H, d, J = 6.6 Hz), 1.13 (3H, d, J = 6.9 Hz), 1.23 (3H, s), 1.43 (3H, s), 1.85−2.17 (5H, m), 2.25 (1H, dd, J = 13.5, 2.5 Hz), 2.34 (1H, d, J = 13.5 Hz), 2.39−2.45 (1H, m), 2.60 (1H, dd, J = 15.3, 2.7 Hz), 2.84 (1H, m), 3.34 (1H, dd, J = 13.5, 2.5 Hz), 3.55 (3H, s), 4.34 (1H, brs), 5.36 (1H, d, J = 2.4 Hz); ^{13}C NMR (62.89 MHz) δ 11.1, 12.2, 19.5, 21.4, 26.2, 28.9, 31.5, 35.1, 35.9, 39.6, 42.5, 43.4, 46.5, 47.6, 55.0, 81.8, 117.5, 147.6, 169.4, 198.6, 209.6.

13-Hydroxy-2-methoxypicras-2-ene-1,12,16-trione (35). To a stirred solution of α-methoxy enone **34** (5 mg, 0.014 mmol) and Et_3N (15 μL, 0.11 mmol) in dry CH_2Cl_2 (0.8 mL) was added TMSOTf (13 μL, 0.072 mmol) at −10 °C under N_2. The reaction mixture was stirred for 30 min at −10 °C and was then quenched with saturated $NaHCO_3$ (50 mL). The mixture was filtered with a thin pad of silica gel which was eluted with EtOAc. The filtrate was concentrated in vacuo. The residue was dissolved in dry CH_2Cl_2 (0.8 mL) and then solid $NaHCO_3$ (9 mg, 0.11 mmol) was added. The reaction mixture was cooled to −20 °C, and then *m*-CPBA (85%, 4 mg, 0.02 mmol) was added. The reaction mixture was stirred for 2 h and then a 1.0 M solution of TBAF in THF (28 mL, 0.028 mmol) was added. The reaction mixture was stirred for 40 min and was then quenched with saturated $Na_2S_2O_3$ (1 mL). The aqueous phase was extracted with CH_2Cl_2 (3 ×). The combined organic extracts were washed with brine, dried ($MgSO_4$), and filtered. Concentration of the filtrate followed by flash column chromatography (1:1 Et_2O/CH_2Cl_2) yielded the alcohol 35 (3.2 mg, 62%) as a white solid: R_f 0.39 (4:1 EtOAc/hexane); mp 202 °C dec; $[\alpha]_D$ = +67.8 (c = 0.2, $CHCl_3$); MS (EI) m/z 376 $[M]^+$; IR 3440 (OH), 1731 (lactone C═O), 1713 (ketone C═O), 1699 (enone C═O), 1634 cm-1 (C═C); ^{1}H NMR (300 MHz) _ 1.14 (3H, d, J = 6.9 Hz), 1.23 (3H, s), 1.29 (3H, s), 1.44 (3H, s), 1.86 (1H, m), 2.00−2.27 (4H, m), 2.34−2.46 (2H, m), 2.54 (1H, dd, J = 16.5, 13.5 Hz), 2.78 (1H, dd, J = 17.7, 8.7 Hz), 2.90 (1H, dd, J = 13.2, 4.2 Hz), 3.57 (3H, s), 3.66 (1H, dd, J = 16.5, 4.2 Hz), 4.25 (1H, t, J = 2.7 Hz), 5.39 (1H, d, J = 2.4 Hz); ^{13}C NMR (75.47 MHz) δ 12.4, 19.5, 24.2, 25.6, 26.1, 28.6, 29.7, 31.4, 35.6, 36.5, 36.9, 42.4, 46.7, 52.1, 55.1, 79.9, 117.8, 147.6, 171.2, 198.7, 211.2; HRMS calcd for $C_{21}H_{29}O_6$ (M + H) 377.1964, found 377.1965.

2,16*β*-Dimethoxypicras-2-ene-1,12-dione (15). To a solution of alcohol **33** (10 mg, 0.029 mmol) in dry THF (8 mL) was added a 1.0 M solution of DIBAL-H in *n*-hexane (87 μL, 0.087 mmol) at −78 °C under N_2. The reaction mixture was stirred for 30 min and was then quenched by slow addition of saturated NH_4Cl (1 mL). The aqueous phase was extracted with EtOAc (3×). The combined organic extracts were dried ($MgSO_4$), and filtered. The filtrate was concentrated under reduced pressure to give the crude lactol. The crude lactol was dissolved in MeOH (10 mL). The reaction solution was cooled to 0 °C and then a catalytic amount of concentrated hydrochloric acid was added. The reaction mixture was stirred for 1 h and was then neutralized with solid $NaHCO_3$. Filtration and concentration afforded the crude mixed acetal which was used in the next reaction without further purification.

To a solution of DMSO (49 μL, 0.69 mmol) in dry CH_2Cl_2 (0.5 mL) was added TFAA (73 μL, 0.52 mmol) at −78 °C under N_2. After 15 min at −78 °C, the reaction mixture was added a solution of crude mixed acetal in dry CH_2Cl_2 (1 mL). The reaction mixture was stirred for 2 h at −78 °C and then Et_3N (158 μL, 1.14 mmol) was added. After the reaction mixture had been warmed to room temperature, it was stirred for 15 min and was then quenched with H_2O (2 mL). The aqueous phase was extracted with CH_2Cl_2 (3 ×). The combined organic extracts were filtered with a thin pad of silica gel which was eluted with Et_2O. The filtrate was concentrated in vacuo to give the crude compound **2-hydroxy-16*β*-methoxypicras-2-ene-1,12-dione**, which was used in the next reaction without further purification.

To a solution of crude **2-hydroxy-16*β*-methoxypicras-2-ene-1,12-dione** in DMF (1 mL) was added CH_3I (36 μL, 0.58 mmol). The reaction mixture was cooled to −20 °C and then NaH (60%, 12 mg, 0.30 mmol) was added. The reaction mixture was stirred for 1 h and was then quenched by slowly addition of MeOH (0.1 mL) followed by addition of saturated NH_4Cl (1 mL). The aqueous phase was extracted with CH_2Cl_2 (3 ×). The combined organic extracts were washed with brine, dried ($MgSO_4$), and filtered. Concentration of the filtrate followed by flash column chromatography (2:1 hexane/EtOAc) produced the α-methoxy enone **15** (7 mg, 65%) as a white solid: R_f 0.50 (2:1 EtOAc/hexane); mp 198−200 °C; $[\alpha]_D$ = +77.2 (c = 1.3, $CHCl_3$); MS (EI) m/z 376 $[M]^+$; IR 1696 (C═O), 1636 cm^{-1} (C═C); ^{1}H NMR (300 MHz) δ 0.92 (3H, d, J = 6.9 Hz), 1.11 (3H, d, J = 6.9 Hz), 1.19 (3H, s), 1.31 (3H, s), 1.42 (1H, dd, J = 13.8, 3.6 Hz), 1.56 (1H, dd, J = 13.9, 4.3 Hz), 1.79 (1H, d, J = 3.3 Hz), 1.82 (1H, d, J = 3 Hz), 1.97 (1H, dd, J = 17.7, 9 Hz), 2.04−2.11 (1H, m), 2.28 (1H, t, J = 13.5 Hz), 2.32−2.38 (1H, m), 2.62 (1H, dd, J = 13.8, 3 Hz), 2.82 (1H, m), 3.18 (1H, dd, J = 13.2, 3 Hz), 3.31 (3H, s), 3.55 (3H, s), 3.71 (1H, t, J = 2.7 Hz), 4.69 (1H, d, J = 3 Hz), 5.33 (1H, d, J = 2.1 Hz); ^{13}C NMR (75.47 MHz) δ 11.2, 12.2, 19.7, 21.6, 26.1, 26.8, 31.7, 35.8, 36.5, 39.8, 43.2, 43.3, 45.9, 47.1, 54.5, 54.9, 69.1, 98.0, 117.4, 147.7, 199.6, 211.9; HRMS calcd for $C_{22}H_{32}O_5$ 376.2249, found 376.2243.

2,12,16*β*-Trimethoxypicrasa-2,12-diene-1,11-dione (37). To a stirred solution of diisopropylamine (8 μL, 0.057 mmol) in dry THF (0.5 mL) was added a 2.5 M solution of *n*-butyllithium in *n*-hexane (22 μL, 0.055 mmol) at −78 °C under N_2. After 15 min at −78 °C, to the reaction mixture was added a solution of α-methoxy enone **15** (10 mg, 0.027 mmol) in dry THF (1 mL). The reaction mixture was stirred for 30 min at −78 °C and then solid MoOPH (115 mg, 0.27 mmol) was added. After 15 min at −78 °C, the reaction mixture was allowed to warm to 0 °C and was then stirred for another 15 min. The reaction was quenched with saturated Na_2SO_3 (2 mL) and diluted with Et_2O (20 mL) and H_2O (3 mL). The aqueous phase was extracted with CH_2Cl_2 (3×). The combined organic extracts were filtered with a thin pad of silica gel which was eluted with EtOAc. Concentration of the filtrate afforded the crude alcohol **14**, which was used in the next reaction without further purification.

To a solution of DMSO (45 μL, 0.64 mmol) in dry CH_2Cl_2 (0.5 mL) was added TFAA (68 μL, 0.48 mmol) at −78 °C under N_2. After 15 min at −78 °C, the reaction mixture was added a solution of crude alcohol **14** in dry CH_2Cl_2 (1 mL). The reaction mixture was stirred for 1.5 h at −78 °C and then Et_3N (147 μL, 1.06 mmol) was added. After the reaction mixture had been warmed to room temperature, it was stirred for another 15 min and was then quenched with H_2O (2 mL). The aqueous phase was extracted with CH_2Cl_2 (3×). The combined organic extracts were filtered with a thin pad of silica gel, which was eluted with EtOAc. Concentration of the filtrate provided the crude α-hydroxy enone, which was used in the next reaction without further purification.

To a solution of the crude α-hydroxy enone in DMF (1 mL) was added CH_3I (34 μL, 0.55 mmol). The reaction mixture was cooled to −20 °C and then NaH (60%, 11 mg, 0.28 mmol) was added. The reaction mixture was stirred for 40 min and was then quenched by slowly addition of MeOH (0.1 mL) followed by addition of saturated NH_4Cl (1 mL). The aqueous phase was extracted with CH_2Cl_2 (3×). The combined organic extracts were washed with brine, dried ($MgSO_4$), and filtered. Concentration of the filtrate followed by flash column chromatography (2:1 hexane/EtOAc) afforded the bis(α-methoxy enone) **37** (5.7 mg, 53%) as a white solid: R_f 0.45 (3:2 EtOAc/hexane); mp 218 °C dec; $[\alpha]_D = +62.4$ ($c = 0.5$, $CHCl_3$); MS (FAB) m/z 405 $[M + H]^+$; IR 1694 (enone C=O), 1639 cm^{-1} (C=C); ^1H NMR (300 MHz) δ 1.05 (3H, s), 1.10 (3H, d, $J = 6.9$ Hz), 1.52 (3H, s), 1.74 (1H, t, $J = 2.4$ Hz), 1.76 (1H, d, $J = 3$ Hz), 1.83 (3H, s), 1.87 (1H, dd, $J = 9.3$, 3.6 Hz), 1.91−1.97 (2H, m), 2.29 (1H, dd, $J = 12$, 4.8 Hz), 2.42 (1H, m), 3.19 (1H, s), 3.36 (3H, s), 3.57 (3H, s), 3.63 (4H, s), 4.79 (1H, d, $J = 2.4$ Hz), 5.27 (1H, d, $J = 2.4$ Hz); ^{13}C NMR (75.47 MHz) δ 12.9, 15.3, 19.6, 22.1, 25.7, 31.0, 31.4, 38.4, 43.9, 44.0, 45.9, 46.1, 54.6, 54.9, 59.1, 69.2, 97.4, 116.2, 139.5, 148.1, 148.3, 193.0, 199.0; HRMS calcd for $C_{23}H_{33}O_6$ (M + H) 405.2277, found 405.2270.

(+)-Quassin (1). A solution of bis(α-methoxy enone) **37** (5 mg, 0.012 mmol) in 60% HOAc aqueous solution (1.6 mL) was refluxed for 25 min under N_2. The reaction mixture was cooled to room temperature and was concentrated in vacuo to give the crude lactol (neoquassin) as a mixture of diastereomers. The crude lactol was dissolved in dry benzene (1 mL) and then Fetizon's reagent (Ag_2CO_3 on Celite) (300 mg) was added. The suspension mixture was refluxed for 2.5 h under N_2 and was then cooled to room temperature. Filtration and concentration of the filtrate followed by flash column chromatography (Et_2O) yielded the (+)-quassin (**1**) (3.8 mg, 79%) as a white solid. Recrystallization from a mixture of Et_2O and CH_2Cl_2 gave colorless crystals, which were identified with the purified commercial material purchased from Apin Chemicals Ltd. (U.K.) by TLC, mp, $[\alpha]_D$, MS, IR, ^1H NMR, and ^{13}C NMR. The constitution of synthetic (+)-quassin (**1**) was corroborated by an X-ray crystallographic analysis.

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Supporting Information Available: Copies of the ^1H and ^{13}C NMR spectra for commercial and synthetic **1** and compounds **8**−**12**, **15**−**27**, **29**−**35**, and **37**. This material is available free of charge via the Internet at http://pubs.acs.org.

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