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Synthetic Approach Toward the Total Synthesis of Kempane Diterpenes via Transannular Diels−Alder Strategy

Franck Caussanel, Keyan Wang, Sreekanth A. Ramachandran, and Pierre Deslongchamps*

Laboratoire de Synthèse Organique, Département de Chimie, Institut de Pharmacologie, Université de Sherbrooke, Sherbrooke, Québec J1H 5N4, Canada

pierre.deslongchamps@usherbrooke.ca

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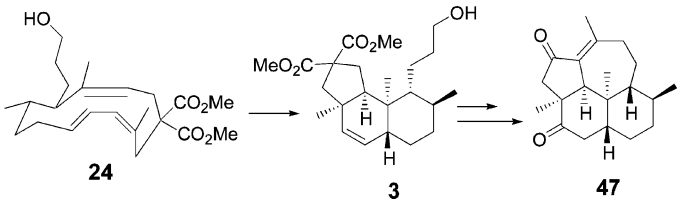

Total syntheses of two new (±)-kempane derivatives **30** and **47** were achieved with transannular Diels−Alder reaction (TADA) serving as the key step for the stereoselective formation of tricyclic [6.6.5] system **3**. This synthetic approach also reveals that the geometry of the C_3 group of such a tricyclic system plays an important role for the formation of the seven-membered kempane skeleton.

Introduction

Two decades ago tetracyclic diterpene kempanes **1** and **2** (Figure 1) were isolated from the defense secretion of termite soldiers *Nasutitermes kempae* and *Nasutitermes octopolis* and their unique structure was determined by NMR studies and X-ray analysis.[1] Their compact structures with numerous contiguous stereogenic centers have made them intriguing and challenging synthetic targets.

The Dauben group[2] described an elegant synthesis of (±)-kempane **2** utilizing the powerful Diels−Alder strategy, while Paquette and co-workers[3] reported an approach to (±)-kempane **1** that includes an efficient palladium-catalyzed [3 + 2] cycloaddition. Even though the synthesis of less-stable natural product **1**[4] was not achieved, this approach culminated in the synthesis of an isomer of **1** where the double bond was conjugated with the ketone. More recent reports toward these natural products include the extensive work from the Burnell group[5] and the IMDA strategy by Hong et al.[6] The only enantioselective approach to this system was reported by Mertz and co-workers in 1993.[7] In this article, we report our work on the synthesis of kempane derivatives utilizing the Transannular Diels−Alder (TADA) strategy for making the functionalized tricyclic core followed by a successful aldol reaction.

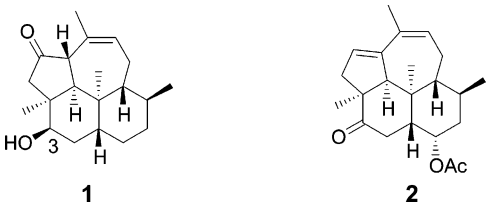

FIGURE 1. Kempane derivatives.

Throughout our long-standing interest in the TADA reaction and its application in natural product synthesis,[8] we envisaged a synthetic strategy that could lead to the total synthesis of kempane **1** using the TADA reaction as the key step. As revealed from the retrosynthesis (Scheme 1), the functionalized tricycle **3** gives access to the tetracyclic framework of kempane **1** by an aldol reaction, which in turn could be obtained by a TADA reaction of macrocyclic triene **4** having the required geometry.

(1) (a) Baker, R.; Walmsley, S. *Tetrahedron* **1982**, *38*, 1899. (b) Prestwich, G. D. *Tetrahedron* **1982**, *38*, 1911. (c) Nakanishi, K.; Goto, T.; Ito, S.; Natori, S.; Nozoe, S. *Natural Products Chemistry*; Oxford University Press: Oxford UK, 1983, Vol. 3, pp 136−138. (d) Prestwich, G. D.; Solheim, B. A.; Clardy, J.; Pielkieweiz, F. G.; Miura, I.; Tanis, S. P.; Nakanish, K. *J. Am. Chem. Soc.* **1977**, *99*, 8082. (e) Prestwich, G. D.; Goh, S. H.; Tho, Y. P. *Experientia* **1981**, *37*, 11.

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(5) (a) Liu, C.; Burnell, D. J. *J. Am. Chem. Soc.* **1997**, *119*, 9584. (b) Bao, G.; Liu, C.; Burnell, D. J. *J. Chem. Soc., Perkin Trans. 1* **2001**, *20*, 2657. (c) Zhao, L.; Burnell, D. J. *Org. Lett.* **2006**, *8*, 155.

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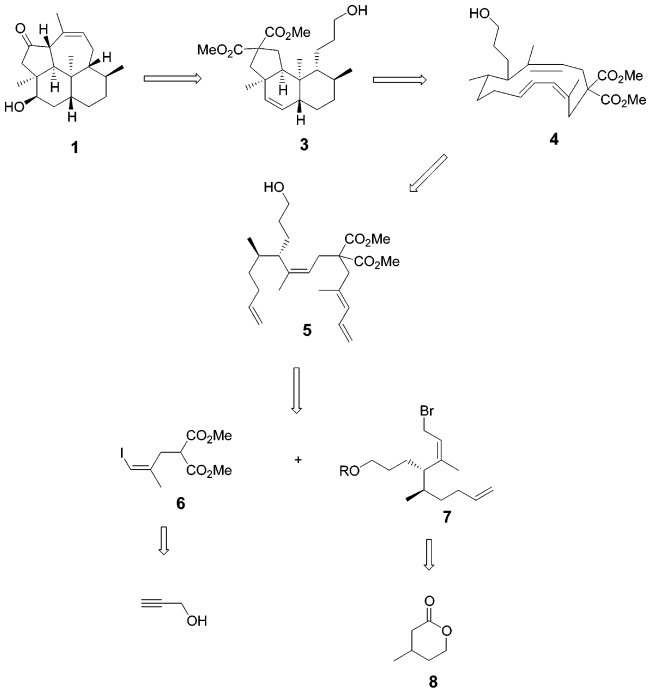
SCHEME 1

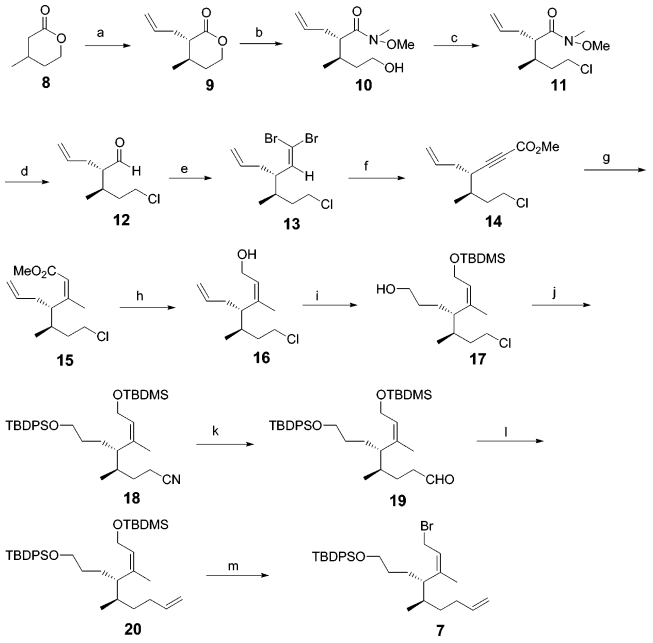


A successful ring-closing metathesis (RCM) on compound **5** would provide access to macrocyclic triene **4**, the former being generated by the coupling of fragments **6** and **7**.

Results and Discussion

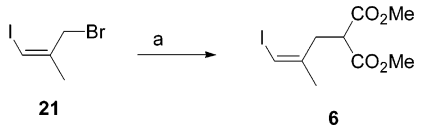
Our investigation toward this goal commenced with the synthesis of fragment **7** (Scheme 2). For this the lactone **8**[9] was allylated by using LDA/allyl bromide to furnish lactone **9**, which was converted to the Weinreb amide **10** with use of *N*,*O*-dimethylhydroxylamine[10] in the presence of trimethyl aluminum. The alcohol **10** was then converted into chloride **11** with PPh_3/NCS and the amide was reduced by DIBAL-H to furnish the aldehyde **12**. The aldehyde **12** was then subjected to the standard Corey−Fuchs conditions[11] resulting in the formation of dibromide **13**, which was then converted to the alkyne ester **14** with *n*-BuLi and methylchloroformate in 95% yield. 1,4-Addition of Gillman's reagent to ester **14** furnished the alkene ester **15** in 76% yield and the ester was further reduced with $LiAlH_4$ to provide the allyl alcohol **16**. Protection of primary alcohol as TBDMS ether followed by oxidation of the double bond with 9-BBN/NaOH/H_2O_2 furnished the chloro alcohol **17** in 96% yield (for two steps). The alcohol **17** was protected as TBDPS ether and the introduction of nitrile with KCN/18-crown-6 afforded the nitrile **18** in near quantitative yield. The nitrile **18** was then reduced with DIBAL-H to furnish the aldehyde **19**,

SCHEME 2 [a]



[a] Reagents and conditions: (a) (i) LDA, THF, −78 °C, (ii) allyl bromide, −78 °C, 6 h, 97%; (b) Me_3Al, MeNOMe·HCl, CH_2Cl_2, 0 °C to rt, 95%; (c) PPh_3, NCS, THF, 0 °C to rt, 17 h, 92%; (d) DIBAL-H, THF, −78 °C, 2 h, 95%; (e) PPh_3, CBr_4, CH_2Cl_2, 0 °C, 30 min, 100%; (f) *n*-BuLi, $ClCO_2Me$, THF, −78 °C, 2 h, 95%; (g) MeLi, CuI, THF, −50 °C, 98%; (h) $LiAlH_4$, THF, 0 °C, 3 h, 95%; (i) (1) Im, TBDMSCl, CH_2Cl_2, rt, 85%, (2) 9-BBN, NaOH, H_2O_2, THF, 0 °C, 2 h, 94%; (j) (i) TBDPSCl, TEA, DMAP, CH_2Cl_2, rt, 2 h, 100%, (ii) KCN, 18-crown-6, CH_3CN, rt, 98%; (k) DIBAL-H, toluene, −78 °C, 94%; (l) *n*-BuLi, PPh_3MeI, THF, rt, 90%; (m) (i) PPTS, EtOH, rt, 20 h, 94%, (ii) MsCl, TEA, LiBr, −45 to 0 °C, 1 h, 99%.

SCHEME 3 [a]



[a] Reagents and conditions: (a) NaH, $CH_2(CO_2Me)_2$, THF:DMF(1:1), rt, 17 h, 77%.

which when subjected to one-carbon homologation with use of the corresponding Wittig reagent afforded the diene **20** in good yield. The allylic ether of diene **20** was selectively removed with PPTS followed by conversion of the alcohol to bromide via mesyl ester furnishing the required fragment **7**, which was used directly for the next step without purification.

The fragment **6** was synthesized by the coupling of iodobromide **21**[12] with methylmalonate in the presence of NaH in THF:DMF solvent mixture (Scheme 3).

Having achieved the synthesis of fragments **6** and **7**, the coupling reaction carried out with NaH as base in THF:DMF solvent mixture at room temperature afforded the acyclic triene **22** in good yield (Scheme 4).

Stille coupling of the iodoester **22** with vinyltributyltin reagent in the presence of Pd(0) in DMF afforded the tetraene ester **23** in quantitative yield. The silyl ether of **23** was then removed by using PTSA in methanol to furnish the tetraene alcohol **23a**.

(8) (a) Toró, A.; Nowak, P.; Deslongchamps, P. *J. Am. Chem. Soc.* **2000**, *122*, 4526. (b) Toró, A.; L'Heureux, A.; Deslongchamps, P. *Org. Lett.* **2000**, *2*, 2737. (c) Germain, J.; Deslongchamps, P. *J. Org. Chem.* **2003**, *67*, 5269. (d) Toró, A.; Deslongchamps, P. *J. Org. Chem.* **2003**, *68*, 6847. (e) Soucy, P.; L'Heureux, A.; Toró, A.; Deslongchamps, P. *J. Org. Chem.* **2003**, *68*, 9983. (f) Beaubien, S.; Deslongchamps, P. *Can. J. Chem.* **2006**, *84*, 29. (g) For a review on TADA reactions see: Marsault, E.; Toró, A.; Nowak, P.; Deslongchamps, P. *Tetrahedron* **2001**, *57*, 4243.

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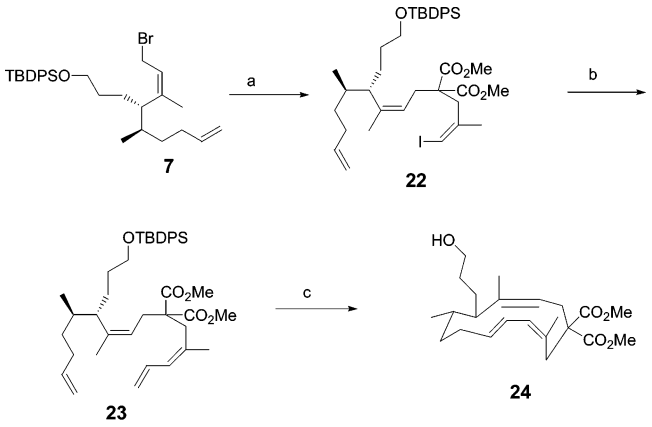
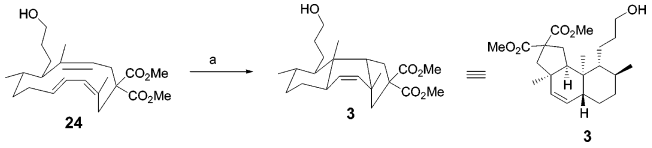
SCHEME 4 [a]



[a] Reagents and conditions: (a) NaH, **6**, THF/DMF, 15 h, 92%; (b) CH_2═$CHSnBu_3$, $Pd_2(dba)_3$, Ph_3P, DMF, 50 °C, 100%; (c) (i) PTSA, MeOH, 93%, (ii) **23a**, Hoveyda−Grubbs catalyst, toluene, reflux, 74%.

SCHEME 5 [a]



[a] Reagents and conditions: (a) sealed tube, Et_3N, toluene, 180 °C, 93%.

Under optimized conditions, the tetraene ester **23a** smoothly underwent macrocyclization by ring-closing metathesis reaction utilizing the Hoveyda−Grubbs catalyst[13] in toluene (0.002 M) to afford the 13-membered macrocyclic triene **24** having a *trans-cis-cis* geometry as the only product in 74% yield.

Our laboratory has previously shown that a 13-membered macrocyclic triene having a *trans-cis-cis* (TCC) geometry will undergo a stereoselective TADA to afford the [*B.C.D*] tricyclic skeleton of 14*β*-hydroxysteroids having *trans-syn-cis* geometry (TSC).[14,8f] In addition, a Lewis acid catalyzed TADA reaction of a 13-membered macrocyclic TCC triene having an activated dienophilic group also affords the tricyclic core having TSC geometry and was successfully applied to the asymmetric total synthesis of (+)-maritimol.[8a]

In this respect the macrocyclic triene **24** synthesized above possesses the required TCC geometry and hence was subjected to the TADA conditions. Under optimized conditions, the macrocyclic triene **24** underwent a TADA reaction in toluene in a sealed tube at 180 °C to afford the TSC tricyclic alcohol **3** having a [6.6.5] ring system as the only product in 93% yield (Scheme 5).

The observed selectivity for the TADA reaction can be explained by considering the preferred transition state for the reaction (Figure 2). Of the two possible conformations, the one where the methyl and R groups are in pseudoequatorial orientation (**A**) is preferred over the other where the groups are pseudoaxial (**B**).

The tricyclic alcohol **3** thus obtained possesses the required functionalities for further transformations (Scheme 6). The

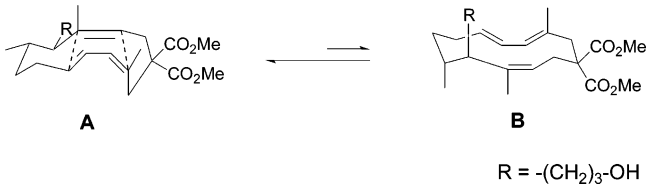
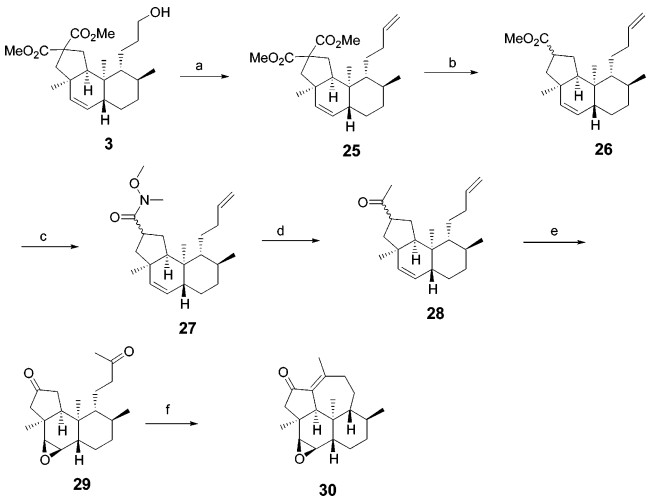


FIGURE 2. Transition states for TADA reaction of **24**.

SCHEME 6 [a]



[a] Reagents and conditions: (a) (i) DMP, CH_2Cl_2, 78%, (ii) $MePPh_3I$, *n*-BuLi, THF, 85%; (b) NaCN, DMF, H_2O, 120 °C, 5 h, 85%; (c) *n*-BuLi, MeONMe·HCl, THF, 0 °C, 65%; (d) MeLi, THF, 0 °C, 89%; (e) (i) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, (ii) $LiAlH_4$, Et_2O, (iii) DMP, $NaHCO_3$, CH_2Cl_2, 35% for 3 steps; (f) K_2CO_3, MeOH, reflux, 36 h, 70%.

alcohol **3** was first oxidized with Dess−Martin periodinane to aldehyde and subsequent Wittig reaction with methyltriphenylphosphonium iodide furnished the diester **25** in 81% overall yield. Decarboxylation of the diester **25** was achieved by using the Krapcho protocol,[15] using NaCN in a refluxing DMF:H_2O mixture to afford the ester diene **26**. The carboxylic ester of **26** was then converted into the Weinreb derivative **27** by using the anion generated from *N*,*O*-dimethyhydroxylamine hydrochloride,[16] which was subsequently transformed into the methyl ketone **28** with MeLi in THF in good yield. The methyl ketone **28** was then subjected to a Bayer−Villiger oxidation by using *m*-chloroperbenzoic acid to afford the cyclopentanone framework, along with the double epoxidation of the olefins. The terminal epoxide was then reduced with $LiAlH_4$ followed by oxidation with Dess−Martin reagent[17] to furnish the diketone **29** in 35% overall yield for 3 steps. A successful aldol reaction performed on **29** with K_2CO_3 as base in refluxing methanol afforded the tetracyclic enone **30** in 70% yield. The structure of **30** was unambiguously confirmed by a single-crystal X-ray diffraction analysis.

At this point a regioselective opening of epoxide **30** followed by a successful deconjugation of enone would lead to the target (±)-kempane **1**. But we were unsuccessful in our attempts to open the epoxide under a variety of conditions; hence we

(13) Kingsbury, J. S.; Harrity, J. P. A.; Bonitatebus, P. J.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1999**, *121*, 791.

(14) (a) Langlois, P.; Soucy, P.; Dory, Y. L.; Deslongchamps, P. *Can. J. Chem.* **1996**, *74*, 129. (b) Ouellet, L.; Langlois, P.; Deslongchamps, P. *Synlett* **1997**, 689.

(15) (a) Krapcho, A. P.; Glynn, G. A.; Grenon, B. *J. Tetrahedron Lett.* **1976**, 3535. (b) Krapcho, A. P.; Weinmaster, J. F.; Eldridge, J. M.; Jahngen, E. G. E.; Lovey, A. J.; Stephens, W. P. *J. Org. Chem.* **1978**, *43*, 138.

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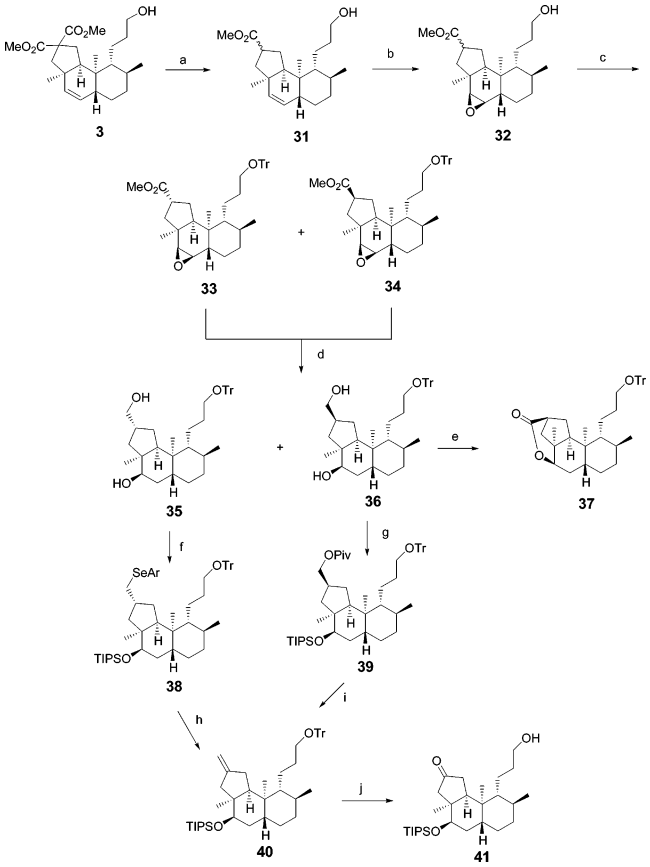
(17) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277.

SCHEME 7 [a]



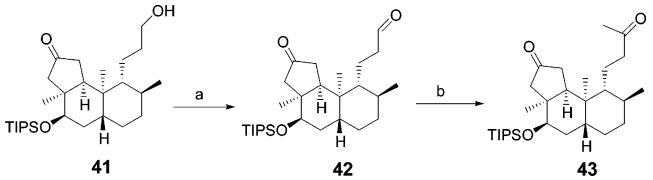
[a] Reagents and conditions: (a) NaCN, DMF, H_2O, 120 °C, 6 h, 81%; (b) *m*-CPBA, CH_2Cl_2, 40 h, rt, 76%; (c) Ph_3CCl, TEA, DMAP, CH_2Cl_2, rt, 12 h, 1:2 (37%:51%); (d) **33**, superhydride, THF, reflux, 12 h, **35** (92%) and **34**, superhydride, THF, reflux, 12 h, **36** (75%); (e) (i) $RhCl_2(PPh_3)_2$, O_2, benzene, (ii) DMAP, CH_2Cl_2, rt, 88%; (f) (i) ArSeCN, Bu_3P, Py, THF, rt, 6 h, (ii) TIPSOTf, Py, CH_2Cl_2, 12 h; (g) *m*-CPBA, Py, CH_2Cl_2, rt, 12 h, 62% over 3 steps; (h) (i) PivCl, Py, rt, 5 h, 92%, (ii) TIPSOTf, lutidine, CH_2Cl_2, rt, 3 h, 97%; (i) (1) $LiAlH_4$, THF, rt, 12 h, 100%, (2a) ArSeCN, Bu_3P, Py, THF, (2b) m-CPBA, Py, CH_2Cl_2, rt, 12 h, 83% over 2 steps; (j) O_3, MeOH:DCM, −78 °C, DMS, rt, 12 h, 85%.

decided to explore another synthetic pathway in which epoxide opening was performed on the tricyclic core prior to the aldol reaction.

For this the alcohol **3** was decarboxylated to ester **31** utilizing the Krapcho protocol (Scheme 7) followed by epoxidation with *m*-CPBA to furnish the epoxy alcohol **32**. The primary alcohol of **32** was then protected as a trityl group, which allowed the separation of the diastereomers **33** and **34**, by column chromatography. Superhydride was found to be the reducing agent of choice for the epoxide opening of both **33** and **34** to yield the diols **35** and **36**, respectively. The regioselectivity of epoxide ring opening was proved by the following transformations: the primary alcohol of diol **36** was selectively oxidized by Rh(II)[18] to the corresponding aldehyde, which underwent lactolization and subsequent oxidation to lactone **37**, the structure of which was proved by single-crystal X-ray diffraction analysis.

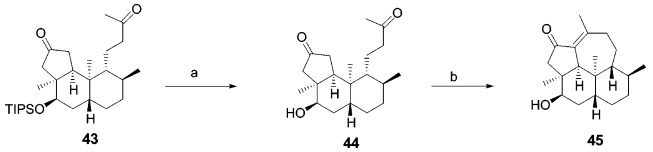
The primary alcohol of diol **35** was then selectively converted into the selenium derivative by using the modified Grieco protocol[19] followed by protection of secondary alcohol as TIPS ether. The resulting tricyclic selenium derivative **38** underwent oxidation with *m*-CPBA and pyridine which promoted elimination to yield the tricyclic olefin **40**. The diastereomeric diol **36** could also be converted to olefin **40** by a similar strategy after appropriate protection of the alcohols.[20] Finally ozonolysis of olefin **40** in MeOH:DCM mixture afforded directly the detritylated tricyclic ketone **41** in 85% yield.

SCHEME 8 [a]



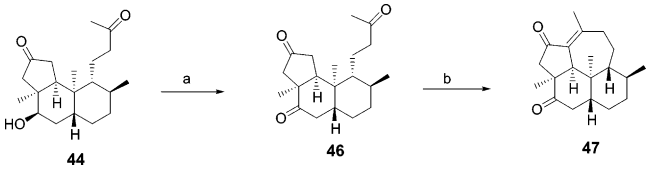
[a] Reagents and conditions: (a) DMP, CH_2Cl_2, rt, 1 h, 80%; (b) (i) MeMgBr, THF, rt, 1 h, 89%, (ii) DMP, CH_2Cl_2, 2 h, 90%.

SCHEME 9 [a]



[a] Reagents and conditions: (a) TBAF, THF, rt, 3 h, 68%; (b) KOH, MeOH, rt, 12 h, 21%.

SCHEME 10 [a]



[a] Reagents and conditions: (a) DMP, CH_2Cl_2, rt, 2 h, 56%; (b) KOH, MeOH, rt, 6 h, 64%.

The tricyclic alcohol **41** was then oxidized with Dess−Martin reagent to the corresponding aldehyde **42** in good yield (Scheme 8). The keto aldehyde **42** thus obtained was exposed to methylmagnesium bromide and subsequent oxidation with Dess−Martin reagent afforded the methyl ketone **43** in excellent yield.

A variety of basic conditions (KOH/MeOH/rt; K_2CO_3/MeOH/reflux; NaOMe/MeOH/rt) were tried for the aldol reaction of diketone **43** but resulted in a very low yield of the tetracylic derivative. Alternatively, removal of the C_3 TIPS ether by TBAF and exposing the resulting alcohol to KOH/MeOH also resulted in a low yield of the conjugated tetracyclic derivative **45** (Scheme 9), the ^{1}H NMR of which was identical to those reported by Paquette.[3] It is interesting to note that Paquette was able to perform an aldol reaction with a tricycle having an α-C_3 protected hydroxyl group, whereas low yields of tetracycle were obtained with a β-C_3 protected or free hydroxyl group.

Having observed the influence of the C_3 hydroxyl group on the aldol reaction, we then oxidized it using Dess−Martin

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(20) Nicolaou, K. C.; Papahatjis, D. P.; Claremon, D. A.; Magolda, R. L.; Dolle, R. E. *J. Org. Chem.* **1985**, *50*, 1440.

reagent to afford the triketone **46**, which when exposed to KOH/MeOH underwent a successful aldol reaction. The conjugated tetracyclic enone **47** was obtained as the only product in good yield (Scheme 10).

Our attempts either to reduce the C_3 ketone selectively or to deconjugate the enone were unsuccessful under a variety of conditions.

Conclusion

In summary, total syntheses of two new (±)-kempane derivatives **30** and **47** along with the Paquette derivative **45** were achieved by using a highly stereoselective TADA reaction followed by a successful aldol reaction. This synthetic strategy has also shown that the success of aldol reaction for the formation of the seven-membered ring of the kempane skeleton was highly influenced by the geometry of the C_3 groups.

Experimental Section

Iodotriene 22: To a stirred suspension of NaH (0.254 g, 6.3 mmol) in THF:DMF (60 mL, 1:1) at 0 °C was added a solution of iodoester **6** (1.97 g, 6.3 mmol) in THF (30 mL) with stirring for 10 min at room temperature. To this was added a solution of bromide **7** (3.0 g, 5.7 mmol) in THF (30 mL) via cannula and the reaction was stirred for 12 h at room temperature. The reaction was quenched by saturated NH_4Cl (10 mL) and extracted with Et_2O:hexane (1:1, 3 × 15 mL), dried, and column chromatographed over silica gel with hexane:EtOAc to provide the iodotriene **22** (4.02 g, 92% over 2 steps). IR ($CHCl_3$, ν, cm^{-1}): 2896, 1733, 1640, 1589. ^1H NMR (300 MHz, $CDCl_3$): δ 7.75−7.25 (m, 10H), 6.05 (d, J = 1.4 Hz, 1H), 5.85−5.65 (m, 1H), 5.22 (t, J = 6 Hz, 1H), 4.96 (d, J = 17 Hz, 1H), 4.90 (d, J = 10 Hz, 1H), 3.70 (s, 3H), 3.68 (s, 3H), 3.65−3.55 (m, 2H), 2.99 (s, 2H), 2.63 (m, 2H), 2.20−2.00 (m, 2H), 1.90−0.80 (m, 8H), 1.78 (d, J = 1.4 Hz, 3H), 1.50 (s, 3H), 1.00 (s, 9H), 0.87 (d, J = 6.8 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.6, 143.2, 140.0, 139.2, 135.5, 134.1, 129.5, 127.6, 121.3, 114.2, 79.4, 64.3, 56.9, 52.5, 46.1, 41.8, 34.8, 33.8, 32.0, 31.6, 30.8, 26.8, 22.7, 18.9, 17.1, 14.1. HRMS (m/z): calcd for $C_{39}H_{55}IO_5Si$ $(M - C_4H_9)^+$ 701.2159, found 701.2148 ± 0.0021.

Tetraene 23: To a degassed and stirred solution of iodotriene **6** (4.02 g, 5.3 mmol) in THF (106 mL) was added vinyltributyltin (4.6 mL, 15.9 mmol) and triphenyl phosphine (0.556 g, 2.1 mmol) followed by $Pd_2(dba)_3$ (0.97 g, 1.0 mmol) and the reaction mixture was stirred at 50 °C for 5 h, water (20 mL) was added to quench the reaction and extracted with Et_2O:hexane (1:1) (3 × 35 mL), and the reraction was dried and column chromatographed over silica gel with hexane:EtOAc to afford the tetraene **23** (3.49 g, 100%). IR ($CHCl_3$, ν, cm^{-1}): 3072, 2952, 1731, 1641, 1590. ^1H NMR (300 MHz, $CDCl_3$): δ 7.70−7.30 (m, 10H), 6.49 (dt, J = 16.8, 11 Hz, 1H), 5.95 (d, J = 11 Hz, 1H), 5.85−5.55 (m, 1H), 5.13 (t, J = 4.8 Hz, 1H), 5.11−4.85 (m, 4H), 3.66 (s, 3H), 3.64 (s, 3H), 3.65−3.50 (m, 2H), 2.90 (s, 2H), 2.60 (s, 2H), 2.15−2.00 (m, 2H), 1.90−0.70 (m, 8H), 1.69 (d, J = 1.4 Hz, 3H), 1.53 (s, 3H), 1.03 (s, 9H), 0.91 (d, J = 6.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.9, 140.4, 139.1, 135.6, 134.1, 133.7, 132.7, 131.2, 129.5, 127.6, 120.8, 116.1, 114.2, 64.3, 57.2, 52.4, 46.2, 35.1, 34.7, 33.7, 31.7, 31.5, 30.8, 26.8, 26.2, 24.8, 22.7, 19.2, 18.9, 17.1, 14.1, 13.6. HRMS (m/z): calcd for $C_{41}H_{58}O_5Si$ $(M - C_4H_9)^+$ 601.3349, found 601.3353 ± 0.0018.

Macrocyclic triene 24: To a stirred solution of tetraene **23** (1.90 g, 2.8 mmol) in methanol (25 mL) was added PTSA (0.11 g, 0.5 mmol) with stirring for 10 h at room temperature. The reaction was quenched by saturated $NaHCO_3$ solution (20 mL) and extracted with CH_2Cl_2 (3 × 15 mL), dried, and column chromatographed over silica gel to furnish the tetraene alcohol **23a** (1.12 g, 93%). IR ($CHCl_3$, ν, cm^{-1}): 3368, 2914, 1731, 1644. ^1H NMR (300 MHz, $CDCl_3$): δ 6.50 (ddd, J = 17, 10.9 Hz, 1H), 5.97 (d, J = 10.9 Hz, 1H), 5.80−5.60 (m, 1H), 5.15 (t, J = 6 Hz, 1H), 5.12−4.88 (m, 4H), 3.69 (s, 3H), 3.67 (s, 3H), 3.58 (td, J = 6.4, 1.6 Hz, 2H), 2.90 (d, J = 2.7 Hz, 2H), 2.60 (dd, J = 6, 1.5 Hz, 2H), 2.18−2.00 (m, 2H), 1.99−1.80 (m, 1H), 1.70−0.94 (m, 7H), 1.69 (s, 3H), 1.52 (s, 3H), 0.91 (d, J = 6.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.9, 140.1, 139.1, 133.6, 132.7, 131.2, 121.0, 116.2, 116.1, 114.3, 63.3, 57.2, 52.4, 46.1, 35.2, 34.6, 33.7, 31.7, 31.5, 30.8, 26.1, 24.7, 18.9, 17.1. HRMS (m/z): calcd for $C_{25}H_{40}O_5$ $(M - H)^+$ 420.2876, found 420.2869 ± 0.0013.

To a stirred solution of tetraene alcohol **23a** (0.87 g, 2.0 mmol) in toluene (1390 mL) was added Hoveyda−Grubbs catalyst (0.132 g, 0.2 mmol) and the reaction mixture was refluxed for 1 h and then cooled to room temperature and vinyl ethyl ether (1 mL) was added to it with stirring for 30 min. The solvent was evaporated off and the residue was column chromatographed over silica gel with hexane:EtOAc to furnish the macrocyclic triene **24** (0.6 g, 74%). IR ($CHCl_3$, ν, cm^{-1}): 3365, 2949, 1735, 1434. ^1H NMR (300 MHz, $CDCl_3$): δ 6.40−6.20 (m, 1H), 6.04 (d, J = 10.7 Hz, 1H), 5.61 (dt, J = 15.4, 5.5 Hz, 1H), 5.15−5.05 (m, 1H), 3.74 (s, 3H), 3.69 (s, 3H), 3.63 (t, J = 5.5 Hz, 2H), 3.08−2.80 (m, 2H), 2.70−2.60 (m, 2H), 2.10−2.00 (m, 2H), 1.80−0.90 (m, 6H), 1.72 (s, 3H), 1.60 (s, 3H), 0.89 (d, J = 6.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.2, 142.6, 135.8, 131.9, 130.7, 127.4, 121.6, 63.3, 57.5, 52.3, 47.4, 35.8, 34.4, 33.3, 33.0, 31.0, 30.5, 30.0, 29.1, 27.0, 24.9, 18.6, 17.0. HRMS (m/z): calcd for $C_{23}H_{36}O_5$ 392.2563, found 392.2556 ± 0.0011.

Tricyclic alcohol 3: To a solution of macrocyclic triene **24** (0.474 g, 1.2 mmol) in toluene (80 mL) was added Et_3N (0.726 mL, 1.2 mmol) and the sealed tube was placed in an oil bath at 180 °C for 17 h. The solvent was evaporated off and the residue was column chromatographed over silica gel with hexane:EtOAc to afford the tricyclic alcohol **3** (0.44 g, 93%). IR ($CHCl_3$, ν, cm^{-1}): 3413, 2934, 1733, 1440. ^1H NMR (300 MHz, $CDCl_3$): δ 5.36 (dd, J = 10, 2.7 Hz, 1H), 5.13 (dd, J = 10, 1.7 Hz, 1H), 3.75 (s, 3H), 3.68 (s, 3H), 3.63−3.40 (m, 2H), 2.36−0.70 (m, 12H), 1.14 (s, 3H), 0.91 (d, J = 6.4 Hz, 3H), 0.77 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.2, 172.4, 134.6, 127.7, 63.6, 57.6, 52.8, 52.6, 51.3, 50.1, 49.4, 42.7, 39.3, 38.3, 36.3, 36.1, 34.6, 34.1, 29.7, 27.2, 24.3, 21.3, 15.9. HRMS (m/z): calcd for $C_{23}H_{36}O_5$ 392.2563, found 392.2560 ± 0.0011.

Tricyclic alkene 25: To a stirred solution of tricyclic alcohol **3** (0.44 g, 1.1 mmol) in CH_2Cl_2 (20 mL) and $NaHCO_3$ (0.141 g, 1.6 mmol) was added Dess−Martin periodinane (0.713 g, 1.6 mmol). The reaction mixture was stirred for 30 min at room temperature and quenched by saturated sodium thiosulfate solution (50 mL) and again stirred for 1 h at room temperature. Extraction with CH_2Cl_2 (3 × 20 mL), drying, and column chromatography over silica gel with hexane:EtOAc furnished the tricyclic aldehyde **3a** (0.343 g, 78%). ^1H NMR (300 MHz, $CDCl_3$): δ 9.76 (t, J = 1.4 Hz, 1H), 5.34 (dd, J = 10, 2.7 Hz, 1H), 5.12 (dd, J = 10, 1.7 Hz, 1H), 3.72 (s, 3H), 3.66 (s, 3H), 2.52−2.30 (m, 2H), 2.35−2.05 (m, 3H), 2.00−0.70 (m, 9H), 1.15 (s, 3H), 0.88 (d, J = 6.4 Hz, 3H), 0.79 (s, 3H).

To a stirred suspension of methyltriphenylphosphonium iodide (0.71 g, 1.7 mmol) in THF (17 mL) at 0 °C was added *n*-BuLi (1.29 mL, 1.7 mmol, 1.36 M in hexane) with stirring for 30 min then warming to room temperature. To this was added a solution of tricyclic aldehyde **3a** (0.343 g, 0.8 mmol) in THF (17 mL) and the resulting solution was stirred for 17 h at room temperature. The reaction was quenched by saturated NH_4Cl solution (20 mL), extracted with Et_2O (3 × 15 mL), dried, and column chromatographed over silica gel with hexane:EtOAc to provide the tricyclic alkene **25** (0.29 g, 85%). IR ($CHCl_3$, ν, cm^{-1}): 2950, 1735, 1639, 1435. ^1H NMR (300 MHz, $CDCl_3$): δ 5.83−5.70 (m, 1H), 5.34 (dd, J = 10, 2.7 Hz, 1H), 5.13 (dd, J = 10, 1.7 Hz, 1H), 5.05−4.90 (m, 2H), 3.73 (s, 3H), 3.67 (s, 3H), 2.37−1.80 (m, 8H), 1.75−0.76 (m, 8H), 1.17 (s, 3H), 0.91 (d, J = 6.4 Hz, 3H), 0.77 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.0, 172.4, 139.5, 134.6, 127.8, 113.8, 57.6, 52.7, 52.6, 51.2, 49.8, 49.3, 42.9, 39.2, 38.3, 36.2, 36.0, 35.2, 34.1, 29.5, 27.9, 27.2, 21.3, 16.1. HRMS (m/z): calcd for $C_{24}H_{36}O_4$ 388.2613, found 388.2622 ± 0.0011.

Tricyclic ester 26: To a stirred solution of tricyclic alkene **25** (0.29 g, 0.7 mmol) in DMF (18 mL) was added NaCN (0.151 g, 3.0 mmol) and 0.9 mL of water and the resulting solution was refluxed at 120 °C for 5 h. The reaction was quenched by saturated $NaHCO_3$ solution (30 mL), extracted with CH_2Cl_2 (3 × 20 mL), dried, and column chromatographed over silica gel with hexane:EtOAc to furnish the tricyclic ester **26** (0.21 g, 85%). IR ($CHCl_3$, ν, cm^{-1}): 2948, 2916, 1735, 1638, 1459. ^1H NMR (300 MHz, $CDCl_3$): δ 5.85−5.71 (m, 1H), 5.31 (dd, J = 10, 1.7 Hz, 1H), 5.25 (s, 1H), 5.20−4.85 (m, 3H), 3.63 (s, 3H), 2.83−2.50 (m, 1H), 2.25−1.30 (m, 10H), 1.28−0.75 (m, 6H), 1.16 (s, 3H), 0.90 (d, J = 6.5 Hz, 3H), 0.80 (s, 3H). HRMS (m/z): calcd for $C_{22}H_{34}O_2$ 330.2559, found 330.2561 ± 0.0010.

Tricyclic amide 27: To a stirred solution of *N*,*O*-dimethylhydroxylamine hydrochloride (0.040 g, 0.4 mmol) in THF (4.5 mL) at 0 °C was added *n*-BuLi (0.61 mL, 0.8 mmol, 1.36 M in hexane) and the resulting solution was stirred for 15 min at 0 °C. To this was added a solution of tricyclic ester **26** (0.091 g, 0.2 mmol) in THF (4 mL), with stirring for 30 min at 0 °C, then the reaction was quenched by saturated NH_4Cl solution (20 mL), extracted with Et_2O (3 × 20 mL), dried, and column chromatographed over silica gel with hexane:EtOAc to furnish the tricyclic amide **27** (0.064 g, 65%). IR ($CHCl_3$, ν, cm^{-1}): 2922, 2867, 1665, 1462, 1442. ^1H NMR (300 MHz, $CDCl_3$): δ 5.83−5.69 (m, 1H), 5.45 (dd, J = 10, 2.0 Hz, 1H), 5.28 (s, 1H), 5.15−4.80 (m, 3H), 3.75 (s, 3H), 3.20 (s, 3H), 2.85−2.60 (m, 1H), 2.33−1.56 (m, 8H), 1.45−0.79 (m, 8H), 1.17 (s, 3H), 0.95 (d, J = 6.4 Hz, 3H), 0.75 (s, 3H). HRMS (m/z): calcd for $C_{23}H_{37}O_2N$ 359.2824, found 359.2827 ± 0.0011.

Tricyclic ketone 28: To a stirred solution of tricyclic amide **27** (0.065 g, 0.1 mmol) in THF (4 mL) at 0 °C was added MeLi (0.335 mL, 0.5 mmol, 1.57 M in Et_2O) with stirring for 15 min at this temperature. The reaction was quenched by saturated NH_4Cl solution (15 mL), extracted with Et_2O (3 × 15 mL), dried, and column chromatographed over silica gel with hexane:EtOAc to afford the tricyclic ketone **28** (0.05 g, 89%). IR ($CHCl_3$, ν, cm^{-1}): 2920, 2865, 1711, 1639, 1442, 1377. ^1H NMR (300 MHz, $CDCl_3$): δ 5.85−5.72 (m, 1H), 5.52 (dd, J = 10, 1.5 Hz, 1H), 5.30 (s, 1H), 5.18−4.83 (m, 3H), 2.91−2.70 (m, 1H), 2.15 (s, 3H), 1.95−1.80 (m, 2H), 1.73−1.26 (m, 10H), 1.20−0.85 (m, 4H), 1.15 (s, 3H), 0.90 (d, J = 6.5 Hz, 3H), 0.77 9s, 3H). HRMS (m/z): calcd for $C_{22}H_{34}O_2$ 314.2610, found 314.2603 ± 0.0009.

Tricyclic diketone 29: To a stirred solution of tricyclic ketone **28** (0.05 g, 0.1 mmol) in CH_2Cl_2 (16 mL) at 0 °C was added $NaHCO_3$ (0.2 g, 2.3 mmol) and *m*-CPBA (0.41 g, 2.3 mmol) with stirring for 17 h at room temperature. The reaction was quenched by 20% aqueous sodium thiosulfate solution (20 mL) and stirred for a further 30 min at room temperature, extracted with CH_2Cl_2 (3 × 30 mL), dried, and column chromatographed over silica gel with hexane:EtOAc to furnish the tricyclic epoxy ketone, which was dissolved in Et_2O (10 mL). The resulting solution was cooled to 0 °C and $LiAlH_4$ (0.020 g, 0.5 mmol) was added with stirring for 1 h The reaction was then quenched by saturated Rochelle salt solution (10 mL) and further stirred for 1 h, extracted with EtOAc (3 × 15 mL), dried. and concentrated. The crude alcohol thus obtained was dissolved in CH_2Cl_2 (5 mL) and Dess−Martin reagent (0.159 g, 0.3 mmol) and $NaHCO_3$ (0.037 g, 0.4 mmol) were added with stirring for 1 h at room temperature. The reaction was quenched by 20% sodium thiosulfate solution (10 mL) and stirred for an additional 1 h, extracted with CH_2Cl_2 (3 × 20 mL), dried, and column chromatographed over silica gel with hexane:EtOAc to afford the tricyclic diketone **29** (0.017 g, 35% over 3 steps). IR ($CHCl_3$, ν, cm^{-1}): 2954, 2923, 1743, 1713, 1256. ^1H NMR (300 MHz, $CDCl_3$): δ 2.95 (d, J = 3.7 Hz, 1H), 2.84 (d, J = 3.7 Hz, 1H), 2.69 (d, J = 18.5 Hz, 1H), 2.54 (ddd, J = 17.5, 12, 5 Hz, 1H), 2.38−1.85 (m, 3H), 2.18 (dd, J = 18.5, 1.6 Hz, 1H), 2.11 (s, 3H), 1.80−1.49 (m, 6H), 1.41 (s, 3H), 1.39−0.98 (m, 3H), 0.93 (s, 3H), 0.88 (d, J = 6.4 Hz, 3H), 0.52 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 216.6, 208.5, 60.3, 58.6, 52.5, 49.3, 48.0, 44.8, 40.0, 38.8, 38.2, 37.8, 35.6, 33.6, 30.0, 29.0, 26.0, 21.6, 21.1, 17.9. HRMS (m/z): calcd for $C_{20}H_{30}O_3$ 318.2195, found 318.2202 ± 0.0009.

Tetracyclic epoxyketone 30: To a stirred solution of diketone **29** (0.010 g, 0.032 mmol) in methanol (7 mL) was added K_2CO_3 (0.021 g, 0.15 mmol) and the resulting solution was refluxed for 36 h. Water (10 mL) was added to quench the reaction and extracted with CH_2Cl_2 (3 × 15 mL), then the reaction was dried and column chromatographed over silica gel with hexane:EtOAc to furnish the tetracyclic epoxyketone **30** (0.006 g, 70%) as a colorless solid crystallized from the hexane:Et_2O mixture. Mp: 42−44 °C. IR ($CHCl_3$, ν, cm^{-1}): 2949, 2920, 1700, 1626. ^1H NMR (300 MHz, $CDCl_3$): δ 2.96 (d, J = 4.5 Hz, 1H), 2.85 (t, J = 4.5 Hz, 1H), 2.70 (d, J = 18.8 Hz, 1H), 2.38−2.30 (m, 2H), 2.29 (d, J = 2.0 Hz, 3H), 2.17 (ddd, J = 11.3, 8.3, 2.0 Hz, 1H), 2.03 (d, J = 18.8 Hz, 1H), 1.97−0.87 (m, 8H), 1.30 (s, 3H), 0.94 (s, 3H), 0.80 (d, J = 6.4 Hz, 3H), 0.70 (dt, J = 10.9 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 205.8, 153.0, 132.8, 59.7, 57.1, 55.5, 50.7, 47.7, 41.7, 37.8, 36.6, 35.4, 34.7, 32.8, 32.1, 27.6, 21.3, 20.6, 20.1, 17.8. HRMS (m/z): calcd for $C_{20}H_{28}O_2$ 300.2089, found 300.2086 ± 0.0009.

Tricyclic ester 31: To a stirred solution of alcohol **3** (1.27 g, 3.2 mmol) in DMF (70 mL) was added NaCN (0.60 g, 12.2 mmol) and water (3.6 mL). The resulting mixture was refluxed for 6 h at 120 °C, quenched by the addition of water (30 mL), extracted with Et_2O (3 × 40 mL), dried, and column chromatographed over silica gel with hexane:Et_2O to provide the tricyclic ester **31** as an inseparable mixture of diasteromers (0.87 g, 81%). IR ($CHCl_3$, ν, cm^{-1}): 3452, 2949, 2921, 2868, 1735, 1437, 1196. ^1H NMR (300 MHz, $CDCl_3$): δ 5.46 (dd, J = 10, 2.5 Hz, 1H), 5.10 (dd, J = 10, 2.0 Hz, 1H), 3.65 (s, 3H), 3.61−3.55 (m, 2H), 2.60−2.45 (m, 1H), 2.05−1.48 (m, 13H), 1.45−1.22 (m, 2H), 1.20 (s, 3H), 1.15 (s, 3H), 1.05−0.98 (m, 1H), 0.92 (d, J = 6.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 177.7, 177.0, 136.4, 135.4, 131.2, 128.0, 64.2, 63.9, 53.9, 51.8, 50.3, 49.7, 47.3, 46.5, 44.9, 42.1, 41.1, 39.5, 39.1, 38.0, 36.3, 34.6, 34.2, 34.1, 34.0, 33.1, 31.7, 31.4, 30.6, 28.3, 27.8, 27.5, 24.6, 24.4, 22.7, 21.5, 21.4, 16.2, 15.7, 14.2. HRMS (m/z): calcd for $C_{21}H_{34}O_3$ 334.2508, found 334.2500 ± 0.0010.

Epoxy alcohol 32: To a stirred solution of ester **31** (0.234 g, 0.7 mmol) in CH_2Cl_2 (6 mL) was added *m*-CPBA (0.242 g, 2.8 mmol) at 0 °C and the resulting solution was stirred for 40 h at room temperature. The reaction was quenched by saturated $NaHCO_3$ solution (10 mL), extracted with CH_2Cl_2 (3 × 10 mL), dried, and column chromatographed over silica gel with hexane:Et_2O to afford the epoxy alcohol **32** as an inseparable mixture of diastereomers (0.185 g, 76%). IR ($CHCl_3$, ν, cm^{-1}): 3442, 2949, 2875, 1734, 1458, 1382, 1172. ^1H NMR (300 MHz, $CDCl_3$): δ 3.65 (s, 3H), 3.57−3.20 (m, 2H), 3.02−2.61 (m, 2H), 2.34 (br s, 1H), 2.28−2.15 (m, 1H), 1.96−1.43 (m, 13H), 1.27 (s, 3H), 1.10−1.00 (m, 2H), 0.89 (d, J = 6.4 Hz, 3H), 0.82 (s, 3H), 0.70−0.55 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 177.3, 175.5, 63.4, 63.3, 60.1, 59.8, 58.9, 58.4, 53.7, 51.6, 51.5, 50.8, 49.6, 48.9, 43.7, 42.3, 42.0, 41.5, 39.3, 38.9, 38.7, 38.5, 36.1, 35.6, 35.5, 34.2, 33.6, 33.5, 32.4, 31.5, 31.3, 30.8, 29.8, 27.0, 26.5, 24.5, 22.6, 21.2, 21.1, 17.5, 17.3, 14.0. HRMS (m/z): calcd for $C_{21}H_{34}O_4$ 350.2457, found 350.2459 ± 0.0010.

Tricyclic esters 33 and 34: To a stirred solution of epoxy alcohol **32** (0.13 g, 0.3 mmol) and pyridine (48 μL, 0.5 mmol) in CH_2Cl_2 (3 mL) was added triphenyl methyl chloride (0.135 g, 0.4 mmol) and DMAP (0.006 g, 0.04 mmol). The resulting solution was stirred for 16 h at room temperature and quenched by water (5 mL), extracted with CH_2Cl_2 (3 × 5 mL), dried, and column chromatographed over silica gel with hexane:Et_2O to furnish the diastereomeric esters **33** (0.081 g, 37%) and **34** (0.113 g, 51%).

Ester 33: IR ($CHCl_3$, ν, cm^{-1}): 2950, 2922, 2870, 1732, 1448, 1383, 1171. ^1H NMR (300 MHz, $CDCl_3$): δ 7.45−7.30 (m, 6H), 7.27−7.10 (m, 9H), 3.58 (s, 3H), 3.02 (t, J = 6.3 Hz, 2H), 2.84 (d, J = 3.9 Hz, 1H), 2.75 (d, J = 3.9 Hz, 1H), 2.29−2.15 (m, 1H), 1.91−1.45 (m, 13H), 1.29 (s, 3H), 1.01−0.95 (m, 1H), 0.91 (d, J = 6.4 Hz, 3H), 0.82 (s, 3H), 0.70−0.62 (m, 1H). ^{13}C NMR (75

MHz, $CDCl_3$): δ 176.9, 144.4, 128.6, 127.7, 126.8, 86.4, 64.3, 59.8, 58.1, 51.5, 50.8, 49.4, 43.9, 41.7, 40.7, 39.0, 38.5, 35.7, 33.5, 31.2, 31.0, 29.7, 26.6, 25.0, 21.1, 17.7. HRMS (*m*/*z*): calcd for $C_{40}H_{48}O_4$ 592.3552, found 592.3548 ± 0.0017.

Ester 34: IR ($CHCl_3$, ν, cm^{-1}): 2950, 2922, 2870, 1732, 1448, 1171, 1072. ^1H NMR (300 MHz, $CDCl_3$): δ 7.45−7.32 (m, 6H), 7.28−7.15 (m, 9H), 3.68 (s, 3H), 3.03−2.92 (m, 2H), 2.85−2.60 (m, 2H), 2.30−2.13 (m, 1H), 1.95−1.40 (m, 13H), 1.30 (s, 3H), 1.05−0.95 (m, 2H), 0.90 (d, J = 6.3 Hz, 3H), 0.85 (s, 3H), 0.75−0.68 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.5, 144.4, 128.6, 127.7, 126.8, 86.4, 64.3, 60.1, 58.9, 53.8, 51.6, 49.0, 42.4, 42.0, 39.3, 38.7, 35.5, 33.5, 32.4, 31.4, 31.1, 27.0, 25.0, 21.2, 17.4. HRMS (*m*/*z*): calcd for $C_{40}H_{48}O_4$ 592.3552, found 592.3542 ± 0.0017.

Tricyclic diol 35: To a stirred solution of epoxy ester **33** (0.081 g, 0.1 mmol) in THF (5 mL) was added superhydride (2.7 mL, 0.2 mmol, 1 M in THF) and the resulting solution was heated for 16 h at 60 °C. The reaction was quenched by water (5 mL), extracted with Et_2O (3 × 10 mL), dried, and column chromatographed over silica gel with hexane:EtOAc to provide the tricyclic diol **35** (0.071 g, 92%). IR ($CHCl_3$, ν, cm^{-1}): 3367, 3022, 2920, 2868, 1448, 1383, 1069. ^1H NMR (300 MHz, $CDCl_3$): δ 7.55−7.40 (m, 6H), 7.33−7.18 (m, 9H), 3.64−3.55 (m, 1H), 3.48−3.33 (m, 2H), 3.25−3.01 (m, 2H), 2.45−2.23 (m, 1H), 2.14−2.04 (m, 2H), 1.82−1.35 (m, 14H), 1.06 (s, 3H), 1.05−0.93 (m, 2H), 0.90 (d, J = 6.3 Hz, 3H), 0.84 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.5, 128.7, 127.6, 126.8, 86.3, 75.0, 69.0, 64.6, 52.3, 50.8, 46.2, 44.4, 38.8, 38.0, 36.1, 34.4, 32.2, 31.9, 31.2, 29.1, 28.5, 24.8, 21.6, 15.9. HRMS (*m*/*z*): calcd for $C_{33}H_{45}O_3$ $(M - C_6H_5)^+$ 489.3368, found 489.3376 ± 0.0014.

Tricyclic diol 36: To a stirred solution of epoxy ester **34** (0.146 g, 0.2 mmol) in THF (5 mL) was added superhydride (4.9 mL, 0.4 mmol, 1 M in THF) and the resulting solution was heated for 16 h at 60 °C. The reaction was quenched by water (5 mL), extracted with Et_2O (3 × 10 mL), dried, and column chromatographed over silica gel with hexane:EtOAc to provide the tricyclic diol **36** (0.125 g, 75%). IR ($CHCl_3$, ν, cm^{-1}): 3305, 3057, 2967, 2869, 1448, 1385, 1073. ^1H NMR (300 MHz, $CDCl_3$): δ 7.51−7.40 (m, 6H), 7.33−7.18 (m, 9H), 3.77−3.65 (m, 2H), 3.61−3.40 (m, 1H), 3.04−2.86 (m, 2H), 2.15−2.10 (m, 1H), 1.98−1.71 (m, 4H), 1.75−1.45 (m, 6H), 1.40−1.20 (m, 4H), 1.12 (s, 3H), 1.10−0.93 (m, 2H), 0.93 (d, J = 6.3 Hz, 3H), 0.86 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.5, 128.7, 127.6, 126.8, 86.3, 75.7, 64.8, 64.5, 55.6, 51.2, 45.1, 40.4, 39.1, 37.1, 36.2, 34.8, 34.3, 32.9, 31.4, 30.3, 28.8, 24.9, 21.7, 16.2. HRMS (*m*/*z*): calcd for $C_{39}H_{48}O_2$ $(M - H_2O)^+$ 548.3654, found 548.3641 ± 0.0016.

Tricyclic ether 39: To a stirred solution of diol **36** (0.129 g, 0.2 mmol) in dry pyridine (1 mL) was added trimethylacetyl chloride (31 μL, 0.2 mmol) at 0 °C and the resulting solution was stirred at room temperature for 5 h. The reaction was quenched by adding cold water (3 mL) and extracted with CH_2Cl_2 (3 × 3 mL), dried, and column chromatographed over silica gel with hexane:Et_2O to afford the alcohol **36a** (0.136 g, 92%). ^1H NMR (300 MHz, $CDCl_3$): δ 7.50−7.47 (m, 6H), 7.34−7.21 (m, 9H), 4.21 (dd, J = 10.4, 8.1 Hz, 1H), 4.04 (dd, J = 10.4, 6.7 Hz, 1H), 3.54−3.40 (m, 1H), 3.04−2.85 (m, 2H), 2.55−2.30 (m, 1H), 1.89−1.48 (m, 12H), 1.37−1.23 (m, 4H), 1.23 (s, 9H), 1.11 (s, 3H), 1.07−0.95 (m, 2H), 0.93 (d, J = 6.3 Hz, 3H), 0.85 (s, 3H). HRMS (*m*/*z*): calcd for $C_{44}H_{56}O_3$ $(M - H_2O)^+$ 632.4229, found 632.4233 ± 0.0019.

To a stirred solution of alcohol **36a** (0.126 g, 0.1 mmol) in CH_2Cl_2 (2.5 mL) was added pyridine (47 μL, 0.5 mmol) and triisopropylsilyl triflate (125 μL, 0.5 mmol) at 0 °C. The reaction was allowed to warm to room temperature during 3 h and quenched by water (3 mL) and extracted with CH_2Cl_2 (3 × 5 mL), dried, and column chromatographed over silca gel with hexane:Et_2O to furnish the tricyclic ether **39** (0.143 g, 97%). IR ($CHCl_3$, ν, cm^{-1}): 2945, 2866, 1728, 1463, 1384, 1285, 160, 1072. ^1H NMR (300 MHz, $CDCl_3$): δ 7.49−7.43 (m, 6H), 7.35−7.20 (m, 9H), 4.05 (d, J = 7.3 Hz, 2H), 3.83−3.75 (m, 1H), 3.02−2.85 (m, 2H), 2.33−2.20 (m, 1H), 1.92−1.55 (m, 9H), 1.53−1.40 (m, 5H), 1.32−1.22 (m, 4H), 1.20 (s, 9H), 1.15 (s, 3H), 1.12 (s, 18H), 1.10−1.00 (m, 3H), 0.91 (d, J = 6.7 Hz, 3H), 0.82 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 178.4, 144.5, 128.7, 127.6, 126.8, 86.3, 75.3, 68.4, 64.4, 55.7, 50.9, 46.1, 39.9, 39.0, 36.2, 36.0, 34.7, 34.4, 33.6, 32.8, 31.4, 31.3, 29.4, 27.5, 25.2, 21.5, 18.5, 18.2, 16.8, 13.1. HRMS (*m*/*z*): calcd for $C_{50}H_{71}O_4Si$ $(M - C_3H_7)^+$ 763.5121, found 763.5140 ± 0.0023.

Tricyclic alkene 40: To a stirred solution of ether **39** (0.143 g, 0.1 mmol) in THF (2 mL) was added $LiAlH_4$ (0.021 g, 0.5 mmol) at 0 °C and the mixture was stirred for 16 h at room temperature. The reaction was quenched with saturated Rochelle salt (2 mL) at 0 °C, extracted with Et_2O (3 × 5 mL), dried, and column chromatographed over silca gel with hexane:Et_2O to afford the alcohol **39a** (0.127 g, 100%). ^1H NMR (300 MHz, $CDCl_3$): δ 7.50−7.44 (m, 6H), 7.35−7.21 (m, 9H), 3.95−3.87 (m, 1H), 3.62 (d, J = 6.7 Hz, 2H), 3.25−3.04 (m, 2H), 2.20−2.06 (m, 1H), 1.85−1.58 (m, 9H), 1.56−1.40 (m, 5H), 1.38−1.23 (m, 5H), 1.16 (s, 3H), 1.12 (s, 18H), 1.10−0.97 (m, 3H), 0.92 (d, J = 6.5 Hz, 3H), 0.83 (s, 3H).

To a stirred solution of alcohol **39a** (0.136 g, 0.2 mmol), *o*-nitrophenylselenocyanate (0.227 g, 1.0 mmol), and pyridine (3 drops) in THF (2.6 mL) was added *n*-tributylphosphine (freshly distilled, 249 μL, 1.0 mmol) dropwise at 0 °C. The reaction mixture was allowed to warm to room temperature during 3 h, and removal of solvent in vacuo followed by column chromatography over silica gel with hexane:Et_2O afforded the selenium derivative that was used for the next step.

The selenium derivative was dissolved in CH_2Cl_2 (15 mL) and pyridine (1.5 mL) and to this was added *m*-CPBA (0.051 g, 0.3 mmol) at −30 °C. The reaction mixture was allowed to warm to room temperature in 4 h and stirred overnight, quenched by saturated $NaHCO_3$ (10 mL), extracted with CH_2Cl_2 (2 × 20 mL), dried, and column chromatographed over silica gel with hexane:Et_2O to afford the tricyclic alkene **40** (0.1 g, 83% over 2 steps). IR ($CHCl_3$, ν, cm^{-1}): 3062, 2928, 2866, 1449, 1383, 1066. ^1H NMR (300 MHz, $CDCl_3$): δ 7.53−7.46 (m, 6H), 7.37−7.21 (m, 9H), 4.75−4.55 (m, 2H), 3.77 (s, 1H), 3.05 (t, J = 6.7 Hz, 2H), 2.80−2.65 (m, 2H), 2.28−2.12 (m, 2H), 1.95−1.50 (m, 8H), 1.42−1.30 (m, 3H), 1.27 (s, 3H), 1.22−1.12 (m, 5H), 1.11 (s, 18H), 1.08−1.00 (m, 1H), 0.96 (d, J = 6.4 Hz, 3H), 0.87 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 151.8, 144.5, 128.7, 127.7, 126.7, 103.1, 86.3, 76.2, 64.5, 54.6, 51.0, 46.9, 45.9, 39.0, 36.9, 36.4, 34.3, 34.2, 32.6, 31.6, 31.2, 29.7, 29.4, 28.6, 24.9, 22.6, 21.6, 18.4, 18.3, 16.2, 14.1, 13.1. HRMS (*m*/*z*): calcd for $C_{45}H_{61}O_2Si$ $(M - C_3H_7)^+$ 661.4441, found 661.4449 ± 0.0020.

Tricyclic alcohol 41: To a stirred solution of alkene **40** (0.065 g, 0.09 mmol) in MeOH (2 mL) and CH_2Cl_2 (3 mL) at −78 °C was bubbled a stream of ozone for 2 min. The color of the solution changed from colorless to pink to blue, and the resulting solution was stirred for 30 min at −78 °C followed by the addition of DMS (1.5 mL) and warmed to room temperature and stirred overnight. The solvent was evaporated off and the crude mixture was purified by column chromatography over silica gel with hexane:EtOAc to furnish the alcohol **41** (0.035 g, 85%). IR ($CHCl_3$, ν, cm^{-1}): 3418, 2943, 2868, 1738, 1464, 1386, 1063. ^1H NMR (300 MHz, $CDCl_3$): δ 3.81 (s, 1H), 3.56 (d, J = 6.2 Hz, 2H), 2.65−2.47 (m, 2H), 2.18−1.95 (m, 3H), 1.85−1.45 (m, 10H), 1.42−1.20 (m, 5H), 1.19 (s, 3H), 1.01 (s, 18H), 0.92 (s, 3H), 0.90 (d, J = 6.5 Hz, 3H), 0.75−0.67 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 217.7, 75.8, 63.6, 53.2, 51.7, 51.0, 44.1, 41.5, 39.1, 36.1, 34.1, 33.9, 33.3, 32.1, 28.2, 28.1, 24.5, 21.4, 18.3, 18.1, 16.5, 12.9. HRMS (*m*/*z*): calcd for $C_{25}H_{45}O_3Si$ $(M - C_3H_7)^+$ 421.3138, found 421.3147 ± 0.0013.

Keto aldehyde 42: To a stirred solution of alcohol **41** (0.01 g, 0.02 mmol) in CH_2Cl_2 (0.3 mL) was added Dess−Martin periodinane (0.011 g, 0.026 mmol) at 0 °C. The resulting solution was stirred at 0 °C for 10 min and warmed to room temperature during 1 h. Removal of solvent in vacuo followed by column chromatography over silica gel provided the keto aldehyde **42** (0.008 g, 80%). IR ($CHCl_3$, ν, cm^{-1}): 2926, 1742, 1738, 1684, 1468, 1386, 1080. ^1H NMR (300 MHz, $CDCl_3$): δ 9.74 (s, 1H), 3.82 (s, 1H), 2.78−

2.59 (m, 1H), 2.58−2.50 (m, 1H), 2.48−2.35 (m, 1H), 2.18−2.08 (m, 1H), 2.02−1.95 (m, 2H), 1.88−1.74 (m, 3H), 1.70−1.50 (m, 3H), 1.43−1.25 (m, 5H), 1.21 (s, 3H), 1.13−1.04 (m, 5H), 1.05 (s, 18H), 0.96 (s, 3H), 0.89 (d, J = 6.4 Hz, 3H), 0.75−0.67 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 217.0, 201.9, 75.7, 53.2, 51.5, 50.6, 45.3, 44.2, 41.4, 39.1, 36.0, 34.0, 33.2, 32.1, 29.6, 28.2, 28.0, 21.3, 19.5, 18.3, 18.1, 16.4, 12.9. HRMS (m/z): calcd for $C_{25}H_{43}O_3Si$ $(M - C_3H_7)^+$ 419.2981, found 419.2973 ± 0.0013.

Diketone 43: To a stirred solution of keto aldehyde **42** (0.009 g, 0.019 mmol) in THF (0.5 mL) at 0 °C was added MeMgBr (15 μL, 0.045 mmol, 3 M in Et_2O) with stirring for 1 h at that temperature. The reaction was quenched by saturated NH_4Cl (2 mL), extracted with Et_2O (3 × 3 mL), dried, and column chromatographed over silica gel with hexane:Et_2O to afford the methyl alcohol **42a** as a mixture of isomers (0.008 g, 89%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.82 (s, 1H), 3.70−3.55 (m, 1H), 2.65−2.48 (m, 2H), 2.20−1.97 (m, 3H), 1.90−1.70 (m, 2H), 1.68−1.58 (m, 3H), 1.57−1.45 (m, 2H), 1.43−1.32 (m, 3H), 1.20−1.25 (m, 3H), 1.21 (s, 3H), 1.17 (d, J = 6.2 Hz, 3H), 1.13−1.06 (m, 2H), 1.12 (s, 18H), 0.96 (s, 3H), 0.92 (d, J = 6.4 Hz, 3H), 0.73−0.62 (m, 1H).

To a stirred solution of alcohol **42a** (0.010 g, 0.021 mmol) in CH_2Cl_2 (0.5 mL) at 0 °C was added Dess−Martin periodinane (0.018 g, 0.042 mmol) with stirring for 10 min at that temperature then slowly warmed to room temperature during 2 h. Removal of solvent in vacuo followed by column chromatography over silica gel with hexane:Et_2O provided the diketone **43** (0.009 g, 90%). IR ($CHCl_3$, ν, cm^{-1}): 2928, 2867, 1742, 1718, 1684, 1459, 1388, 1174, 1078. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.82 (s, 1H), 2.70−2.50 (m, 3H), 2.48−2.30 (m, 1H), 2.20−2.12 (m, 1H), 2.10 (s, 3H), 2.05−1.85 (m, 2H), 1.85−1.45 (m, 6H), 1.42−1.22 (m, 5H), 1.20 (s, 3H), 1.15−1.10 (m, 3H), 1.05 (s, 18H), 0.95 (s, 3H), 0.88 (d, J = 6.4 Hz, 3H), 0.70−0.62 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 217.2, 208.7, 75.8, 53.2, 51.4, 50.6, 45.0, 44.2, 41.5, 39.1, 36.1, 34.2, 33.2, 32.1, 29.9, 28.2, 28.0, 21.4, 18.3, 18.1, 16.3, 12.9. HRMS (m/z): calcd for $C_{26}H_{45}O_3Si$ $(M - C_3H_7)^+$ 433.3138, found 433.3148 ± 0.0013.

Keto alcohol 44: TBAF (2 mL, 0.14 mmol, 1 M in THF) was added to diketone **43** (0.035 g, 0.07 mmol) at 0 °C neat and the mixture was stirred at room temperature for 3 h, quenched by saturated NH_4Cl solution (5 mL), extracted with Et_2O (3 × 8 mL), dried, and column chromatographed over silica gel with hexane:Et_2O to afford the alcohol **44** (0.013 g, 68%). IR ($CHCl_3$, ν, cm^{-1}): 3414, 2954, 2926, 2874, 1738, 1716, 1652, 1456, 1386, 1172. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.69−3.55 (m, 1H), 2.70−2.30 (m, 14H), 2.11 (s, 3H), 2.10−1.68 (m, 6H), 1.66−1.05 (m, 8H), 1.20 (s, 3H), 0.95 (s, 3H), 0.88 (d, J = 6.4 Hz, 3H), 0.80−0.65 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 218.4, 208.8, 74.1, 53.6, 51.0, 50.5, 45.0, 43.5, 41.0, 39.1, 35.8, 34.1, 33.6, 31.7, 29.9, 28.0, 27.5, 21.4, 20.7, 16.3. HRMS (m/z): calcd for $C_{20}H_{32}O_3$ 320.2351, found 320.2344 ± 0.0010.

Tetracyclic alcohol 45: To a stirred solution of keto alcohol **44** (0.005 g, 0.015 mmol) in methanol (5 mL) was added KOH (0.02 g, 0.3 mmol) and the mixture was stirred for 48 h at room temperature. Solvent was removed and saturated NH_4Cl solution (2 mL) was added, then the reaction was extracted with Et_2O (3 × 5 mL), dried, and column chromatographed over silica gel with hexane:EtOAc to afford the tetracyclic alcohol **45** (0.001 g, 21%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.06 (dd, J = 8.3, 8.0 Hz, 1H), 2.60 (d, J = 18.2 Hz, 1H), 2.45−2.35 (m, 1H), 2.33 (s, 3H), 2.20−2.10 (m, 1H), 2.02 (d, J = 18.2 Hz, 1H), 1.80−1.20 (m, 11H), 1.15 (s, 3H), 0.95−0.85 (m, 1H), 0.90 (s, 3H), 0.77 (d, J = 6.4 Hz, 3H), 0.75−0.65 (m, 1H). HRMS (m/z): calcd for $C_{20}H_{30}O_2$ 302.2246, found 302.2249 ± 0.0009.

Triketone 46: To a stirred solution of alcohol **44** (0.009 g, 0.028 mmol) in CH_2Cl_2 (0.5 mL) at 0 °C was added Dess−Martin periodinane (0.124 g, 0.056 mmol) with stirring for 10 min at that temperature and then warming to room temperature during 2 h. Removal of solvent in vacuo followed by column chromatography over silica gel with hexane:Et_2O provided the triketone **46** (0.005 g, 56%). IR ($CHCl_3$, ν, cm^{-1}): 2923, 1744, 1724, 1705, 1460, 1393, 1172, 1105. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.20 (d, J = 18.8 Hz, 1H), 2.75−2.55 (m, 3H), 2.48−2.30 (m, 2H), 2.20−2.10 (m, 2H), 2.13 (s, 3H), 1.89 (d, J = 18.8 Hz, 1H), 1.85−1.75 (m, 2H), 1.72−1.60 (m, 2H), 1.45 (s, 3H), 1.43−1.28 (m, 3H), 1.24 (s, 3H), 1.10−0.95 (m, 1H), 0.89 (d, J = 6.3 Hz, 3H), 0.66−0.50 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 214.8, 212.8, 208.2, 55.2, 50.5, 48.6, 44.7, 41.3, 41.1, 40.7, 39.7, 35.4, 33.8, 30.0, 29.6, 28.5, 26.8, 21.8, 21.1, 16.3. HRMS (m/z): calcd for $C_{20}H_{30}O_3$ 318.2195, found 318.2202 ± 0.0009.

Tetracyclic ketone 47: To a stirred solution of triketone **46** (0.005 g, 0.0015 mmol) in methanol (5 mL) was added KOH (0.02 g, 0.3 mmol) and the resulting solution was stirred for 6 h at room temperature. Solvent was evaporated off and saturated NH_4Cl (2 mL) was added, then the reaction was extracted with Et_2O (3 × 5 mL), dried, and column chromatographed over silica gel with hexane:Et_2O to furnish the tetracyclic ketone **47** (0.003 g, 64%). IR ($CHCl_3$, ν, cm^{-1}): 2919, 2865, 1702, 1682, 1626, 1422. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.79 (d, J = 18.2 Hz, 1H), 2.65−2.42 (m, 3H), 2.36 (s, 3H), 2.30−2.20 (m, 1H), 2.15−2.05 (m, 1H), 2.06 (d, J = 18.2 Hz, 1H), 1.96−1.85 (m, 1H), 1.84−1.70 (m, 1H), 1.43−1.20 (m, 3H), 1.15 (s, 3H), 1.08−0.95 (m, 1H), 0.93−0.85 (m, 1H), 0.82 (d, J = 6.4 Hz, 3H), 0.80 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 214.1, 203.5, 155.5, 131.3, 62.0, 50.6, 48.5, 47.9, 40.9, 38.8, 37.3, 36.9, 35.4, 31.3, 29.6, 25.8, 20.5, 20.4, 20.2, 15.0. HRMS (m/z): calcd for $C_{20}H_{28}O_2$:300.2089, found 300.2091 ± 0.0009.

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Supporting Information Available: Copies of ^{1}H NMR for all new compounds and CIF files and ORTEP diagram for compounds **30** and **37**. This material is available free of charge via the Internet at http://pubs.acs.org.

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