JOC Article

Cascade Polycyclization: Exploration of a Convergent Route to Access Various Tricyclic and Tetracyclic Products Related to Sterols

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The expedient synthesis of tricyclic and tetracyclic compounds via a cascade polycyclization methodology is described. Nazarov substrates (II) containing two Michael acceptors and a cyclohexenone ester (I) underwent cycloaddition followed by intramolecular 1,4-addition to furnish, in a highly stereoselective manner, tricyclic and tetracyclic products (III). Such compounds are interesting intermediates for the synthesis of polycyclic natural and unnatural products.

Introduction

Tricyclic and tetracyclic compounds are among the more ubiquitous structural frameworks found in natural products. Many such compounds, particularly steroids, diterpenes, and triterpenes, elicit important pharmacological activities, for which they still find widespread use. Despite this, few *general* methods have thus far been developed to allow access to such structures.[1] We report herein a general and convergent method for the synthesis of tricyclic and tetracyclic intermediates.

Several years ago, we reported a stereocontrolled synthesis of *cis*-decalins.[2,3] Subsequently, we also disclosed our synthetic approach to access the tetracyclic product **3** by using the reaction between 2-carbomethoxy-2-cyclohexenone[4] (**1**) (Scheme 1) and the Nazarov substrate[5] **2**. Under basic conditions, **3** was obtained as the sole product via a cascade of double-Michael-aldol condensation or the so-called anionic polycyclization reaction.[6] Similarly, the reaction between the chiral Nazarov substrate **5** and the optically active cyclohexenone **4** yielded the tricyclic intermediate **6**, which could be converted to 14-β-hydroxysteroids **7** bearing a β-OBz group at C-17 (steroid numbering) by an intramolecular aldol condensation under basic conditions.[7,8] We have recently pointed out[9] that the intramolecular aldol reaction seems to be very sensitive to the nature of the functionality on the Nazarov substrate, particularly at C-17. Even though specific methods were developed[10] to effect the aldol reaction, none were found to be of general utility because of the reversibility of this reaction. This prompted us to investigate the closure of the C ring using a Michael reaction.[11,12] This alternative method should give access to many tricyclic and tetracyclic intermediates. We have, therefore, prepared the Nazarov key intermediates **15**, **27**, **41**, **53**, **58**, **81**, and **82** and studied their condensation with enone esters **1** and **60**. We wish to report herein on the results of this exploratory investigation.[13]

Results and Discussion

The synthesis of the Michael acceptor Nazarov substrate **15** (Scheme 2) was initiated by the TMSCl/HMPA-catalyzed conjugate addition[14] of the cuprate reagent derived from 4-bromobutene on the cyclopentenone **8** to afford the cyclopentanone **9**. The olefin was oxidized with ozone to yield the aldehyde, which was protected in situ as a dimethylacetal **10**. The cyclopentanone was successfully dehydrogenated by a palladium-catalyzed reaction[15] to yield the cyclopentenone **11** in 50% yield along with

(1) (a) ApSimon, J. *The Total Synthesis of Natural Products*; John Wiley and Sons: New York, 1984, Vol. 6, pp 1−139. (b) Blickenstaff, R. T.; Ghosh, A. C.; Wolf, G. C. *Total Synthesis of Steroids, Organic Chemistry, A Series of Monographs, vol. 30*; Academic Press: New York, 1974. (c) Akhrem, A. A.; Titov, Y. A. *Total Steroid Synthesis*; Plenum Press: New York, 1970.

(2) Lavallée, J.-F.; Deslongchamps, P. *Tetrahedron Lett.* **1988**, *29*, 5117.

(3) (a) Lavallée, J.-F.; Spino, C.; Ruel, R.; Hogan, K. T.; Deslongchamps, P. *Can. J. Chem.* **1992**, *70*, 1406. (b) Ruel, R.; Hogan, K. T.; Deslongchamps, P. *Synlett* **1990**, 516.

(4) Liotta, D.; Bomum, R.; Puleo, G.; Bayer, C.; Kezar, H. S. *J. Org. Chem.* **1981**, *46*, 2920.

(5) Nazarov, I. N.; Zauyalou, S. I. *Obshch. Khim.* **1953**, *23*, 1703.

(6) Lavallée, J.-F.; Deslongchamps, P. *Tetrahedron Lett.* **1988**, *29*, 6033.

(7) Ruel, R.; Deslongchamps, P. *Tetrahedron Lett.* **1990**, *31*, 3961.

(8) Ruel, R.; Deslongchamps, P. *Can. J. Chem.* **1992**, *70*, 1939.

(9) Yang, Z.; Shannon, D.; Truong, V. L.; Deslongchamps, P. *Org. Lett.* **2002**, *4*, 4693.

(10) Chapdelaine, D.; Belzile, J.; Deslongchamps, P. *J. Org. Chem.* **2002**, *67*, 5669.

(11) For a review on Michael reaction, see: Bergmann, E. D., Ginsburg, D.; Pappo, R. *Org. React.* **1967**, *10*, 179.

(12) For a review on the intramolecular version, see: Little, R. D.; Masjedizadeh, M. R.; Wallquist, O.; McLoughlin, J. I. *Org. React.* **1995**, *47*, 315.

(13) For other investigations in this area, see: (a) Lepage, O.; Deslongchamps, P. *J. Org. Chem.* **2003**, *68*, 2183. (b) Lepage, O.; Stone, C., Deslongchamps, P. *Org. Lett.* **2002,** *4*, 1091.

(14) (a) Horiguchi, Y.; Matsuzawa, S.; Nakamura, E.; Kuwajima, I. *Tetrahedron Lett.* **1986**, *27*, 4025. (b) Nakamura, E.; Matsuzawa, S.; Horiguchi, Y.; Kuwajima, I. *Tetrahedron Lett.* **1986**, *27*, 4029.

(15) Shvo, Y.; Arisha, A. H. I. *J. Org, Chem.* **1998**, *63*, 5640.

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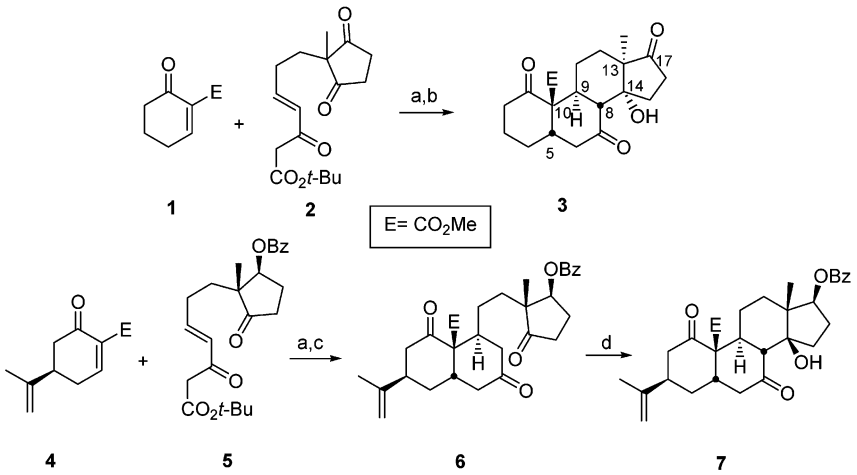
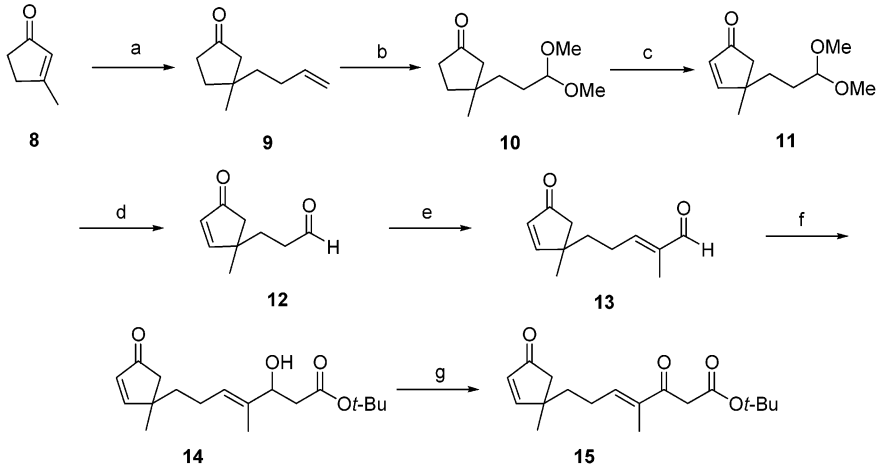
SCHEME 1[a]



[a] Reagents and conditions: (a) Cs_2CO_3, CH_2Cl_2; (b) *p*-TsOH, C_6H_6, reflux, 47% (2 steps); (c) *p*-TsOH, C_6H_6, reflux, 60% (2 steps); (d) Cs_2CO_3, CH_3CN, reflux, 32%.

SCHEME 2[a]

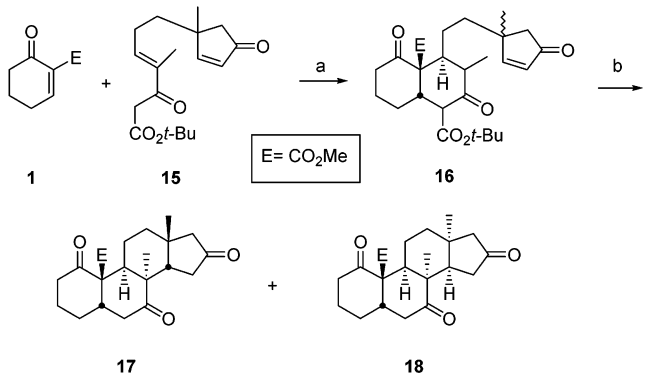


[a] Reagents and conditions: (a) (i) Mg, 4-bromobutene, CuBr DMS, TMSCl, HMPA, THF −78 °C to rt, (ii) AcOH, 97%; (b) (i) O_3, CH_2Cl_2-MeOH, −78 °C, (ii) DMS, −78 °C to rt, (iii) *p*-TsOH, 72%, (90% corr); (c) $Pd(OAc)_2$, $(EtO)_2P(O)$-allyl, Na_2CO_3, THF, reflux, 50%, (100% corr); (d) AcOH−H_2O, 50 °C, 92%; (e) $P(Ph)_3C(Me)CHO$, C_6H_6, reflux, 65%; (f) Zn, $BrCH_2CO_2t$-Bu, THF, 0 °C, 46% (85% corr); (g) Dess−Martin, CH_2Cl_2, 0 °C to rt, 84%.

50% recovered starting material. The reaction curiously stopped at 50% conversion, and all attempts to drive it to completion were unsuccessful. Alternative approaches[16] to obtain the enone by other common methods were either unsuccessful or merely led to complex mixtures. The acetal was hydrolyzed under acidic condition to give the unstable aldehyde **12,** which was immediately submitted to Wittig olefination conditions with the stabilized phosphorane reagent to afford the α,*β*-unsaturated aldehyde **13**. Addition of the Reformatsky reagent derived from *tert*-butyl bromoacetate furnished the alcohol **14**. Further oxidation with Dess−Martin periodinane[17] yielded the *γ*,*δ*-unsaturated *β*-ketoester **15**.

The cyclization of the Nazarov substrate **15** (Scheme 3) was achieved with the activated cyclohexenone **1** under

SCHEME 3[a]



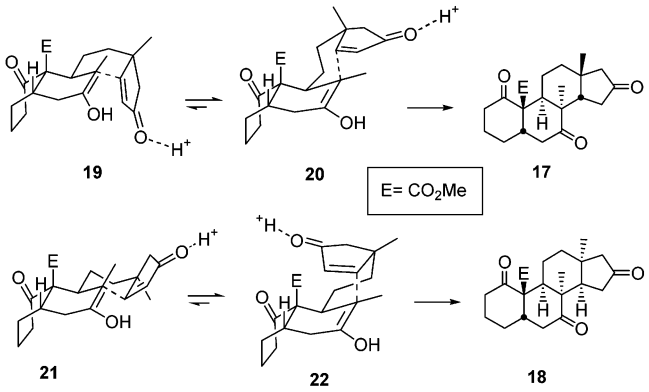
[a] Reagents and conditions: (a) Cs_2CO_3, CH_2Cl_2; (b) *p*-TsOH, C_6H_6, reflux, 40% of **17** and 40% of **18**.

basic condition to yield the tricyclic compound **16** as a mixture of diastereoisomers. This result implies that the

(16) Reaction such as α-bromination−dehydrobromination, α-selenation−oxidation−selenoxide elimination. Standard Pd^{2+} enol ether oxidation, DDQ silyl enol ether oxidation, cupric bromide dehydrogenation, α-ketosulfoxide elimination.

(17) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4156.

SCHEME 4

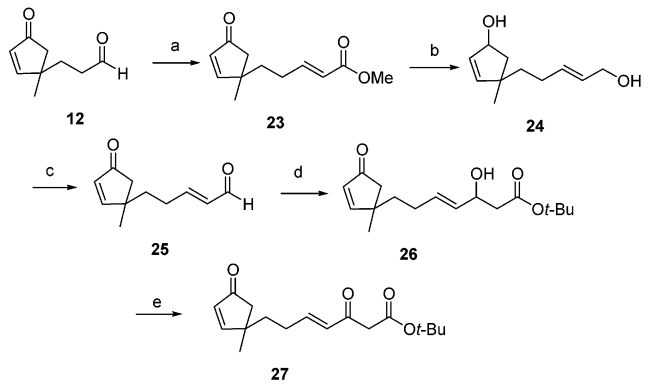


ring D enone is not sufficiently electrophilic to trap the $\Delta^{7,8}$ enolate that is produced in situ after the first cycloaddition step. To achieve this step would probably require a more activated electrophile. Attempts at dealkoxycarbonylation of the *tert*-butyl ester under acidic conditions furnished directly, to our surprise, the corresponding tetracyclic intramolecular Michael adducts **17** and **18**. Each isomer was isolated in 40% overall yield, and their three-dimensional structures were ascertained by single-crystal X-ray diffraction crystallography. The formation of these two racemic diastereoisomers in a 1:1 ratio is, of course, due to the complete lack of facial selectivity in the course of the condensation of **15** with the enonester **1**. It is noteworthy that the 8α-methyl group found in **17** and **18** have the reversed relative stereochemistry compared to that found in natural di- and triterpenes. Inspection of molecular models of the possible transition states **19**−**22** (Scheme 4) reveals that the forming carbon−carbon bond must be the result of a pseudoaxial attack of the enol in both cases in order to provide the maximum orbital overlap. The preferred conformations **20** and **22** must therefore lead to the attack of the enol from its *β*-face giving the α-configuration for the 8-methyl group in the cyclized products. Conformations **19** and **21** would have led to the 8*β*-methyl products. The observed *cis* C/D ring junction can be explained as a result of a sterically more suitable orbital alignment between the enol and the enone.

We then decided to look at the effect of the methyl group on the reactivity of the $\Delta^{7,8}$ enol, since its presence could be essential for the reaction to proceed. To this end, the Nazarov substrate **27** lacking such a methyl group was synthesized (Scheme 5).[18] The synthesis was carried out starting from the aldehyde **12,** which was reacted with the stabilized phosphorane to afford the α,*β*-unsaturated ester **23**. The ester was reduced to the diol **24** and subsequently oxidized to the α,*β*-unsaturated aldehyde **25**. The *γ*,*δ*-unsaturated *β*-ketoester **27** was obtained by the same alkylation−oxidation sequence already described.

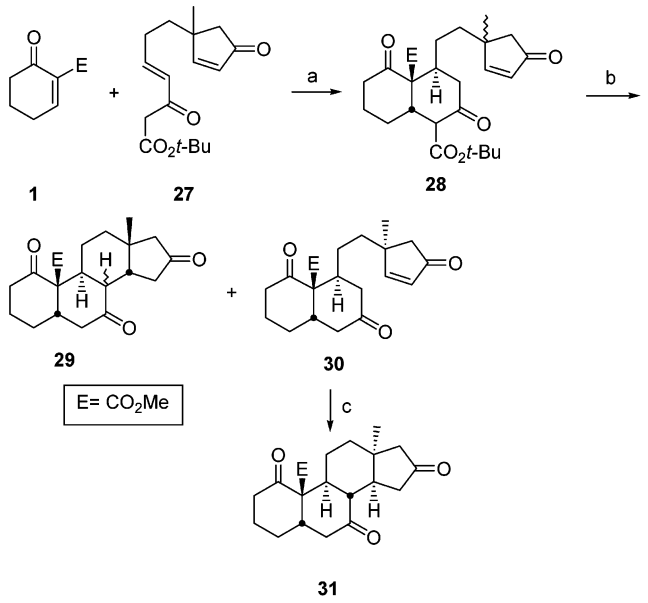
When subjected to the cyclization conditions with cyclohexanone **1** (Scheme 6), the Nazarov substrate **27** yielded the tricyclic product **28** as a mixture of racemic diastereoisomers. On the other hand, when submitted to the acid-catalyzed dealkoxycarbonylation−cyclization reaction, only the tetracycle **29** was isolated as an inseparable epimeric mixture[19] at C-8 (50% overall yield) along with the dealkoxycarbonylated 13α-methyl tricycle **30** in

SCHEME 5[a]



[a] Reagents and conditions: (a) $P(Ph)_3CHCO_2Me$, C_6H_6, reflux, 72%; (b) DIBAL-H, CH_2Cl_2−hexane, −78 °C, 94%; (c) Dess−Martin, CH_2Cl_2, 63%; (d) Zn, $BrCH_2CO_2t$-Bu, THF, 0 °C, 63%; (e) Dess−Martin, CH_2Cl_2, 0 °C to rt, 68%.

SCHEME 6[a]



[a] Reagents and conditions: (a) Cs_2CO_3, CH_2Cl_2; (b) *p*-TsOH, C_6H_6, reflux, 50% of **29** and 20% of **30** (2 steps); (c) *p*-TsOH, toluene, reflux, 100%.

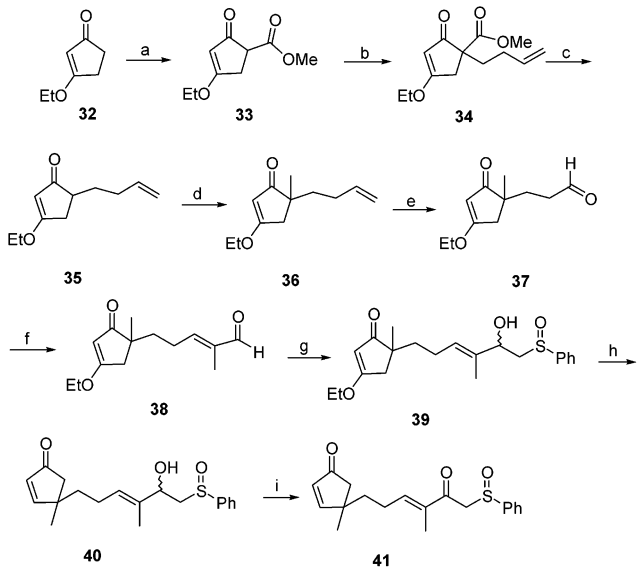
20% overall yield. The latter was cyclized when treated with catalytic amount of *p*-TsOH at the higher temperature of refluxing toluene to afford the 13α-methyl tetracycle **31** in quantitative yield. The three-dimensional structure of this new tetracyclic isomer **31** was ascertained by single-crystal X-ray diffraction crystallography.

The X-ray crystallographic data demonstrates that the tetracycle **31** has the 13α-methyl and 8*β*-H stereochemistry. If the previous results are taken into account (Schemes 3 and 4), it is likely that the first tetracycle formed from **30** must be the 8α-H isomer, which subsequently epimerizes in situ to the more stable *cis-anti-trans-anti-cis* tetracycle **31** resulting in the 8*β*-H stereochemistry. The cyclization results indicate that the

(18) We wish to thank Suzanne Girard for the synthesis of Nazarov substrate **27**.

(19) The mixture was characterized by ^1H NMR only.

SCHEME 7[a]



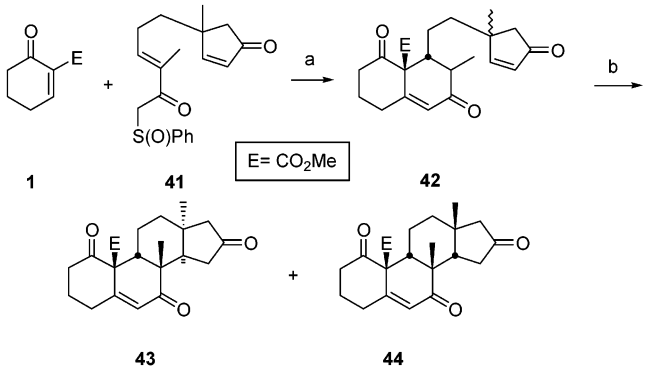
[a] Reagents and conditions: (a) LDA, methylcyanoformate, THF, −78 °C, 60%; (b) KH, bromobutene, DMF, 77%; (c) KOH, EtOH, reflux, 74%; (d) LDA, MeI, THF, −78 °C, 81%; (e) (i) O_3, Sudan 3, CH_2Cl_2, −78 °C, (ii) PPh_3, −78 °C to rt, 90%; (f) $P(Ph)_3C(Me)CHO$, C_6H_6, reflux, 76%; (g) CH_3-S(O)-Ph, LDA, THF, −78 °C; 55%; (h) DIBAL-H, CH_2Cl_2, −78 °C, 63%; (i) Dess−Martin, CH_2Cl_2, 0 °C to rt, 89%.

presence of an additional methyl group at C-8 facilitates the last Michael step from **16,** since a higher temperature is necessary to convert **30** into **31**. This result can be explained either by the fact that a tetrasubstituted enol would be more nucleophilic (thus more reactive) than a trisubstituted one[20] or that it would have a longer half-life once produced in situ. Moreover, the formation of **31** requires a temperature higher than that for **29**. This can be attributed to additional steric interaction generated by approaching the B and D rings in the Michael addition transition state leading to **31** (cf. **22**) by comparison with that of **29** (cf. **20**).

Since the products of the intramolecular Michael addition of γ,δ-unsaturated β-ketoester always possess the 8α-methyl stereochemistry, we sought to contrive means of inverting the stereochemical outcome of this reaction. It was found some years ago in our laboratories[21] that when the β-ketoester moiety of the Nazarov substrate is replaced by a β-ketosulfoxide, the double-Michael cycloaddition with an activated cyclohexenone yielded stereospecifically decalins with the substituent at C-9 in the opposite configuration. On the basis of this result we speculated that the β-ketosulfoxide Nazarov substrate **41** (Scheme 7) should give the inverted stereochemistry at C-9 (β configuration of the hydrogen) and that should invert the stereochemistry at C-8 to yield the 8β-methyl tetracycles, assuming that the B/C ring junction will still be formed in a *cis* fashion.

Accordingly, the β-ketosulfoxide **41** (Scheme 7) was prepared starting from the acylation of the known enolether protected 1,3-cyclopentandione **32**[22] using methyl cyanoformate[23] to afford the β-ketoester **33**. The potassium anion of **33** was alkylated with 4-bromobutene to yield the butenyl-β-ketoester **34**. The ester was hydrolyzed and the acid salt was decarboxylated to yield

SCHEME 8[a]



[a] Reagents and conditions: (a) Cs_2CO_3, CH_2Cl_2; (b) *p*-TsOH, C_6H_6, reflux, 13% of **43** and 13% of **44** (2 steps).

the butenyl cyclopentenone **35**. The cyclopentenone was α-methylated to yield **36**. The terminal olefin was selectively oxidized[24] with ozone and the resulting aldehyde **37** was reacted with the stabilized phosphorane to yield the α,β-unsaturated aldehyde **38**. Methylphenyl sulfoxide lithium salt[25] was added to the latter to yield the hydroxysulfoxide **39**. The carbonyl of the enone was reduced to the alcohol followed by acid hydrolysis to afford directly the cyclopentenone **40**. The alcohol was finally oxidized by Dess−Martin periodinane to yield the γ,δ-unsaturated β-ketosulfoxide **41**.

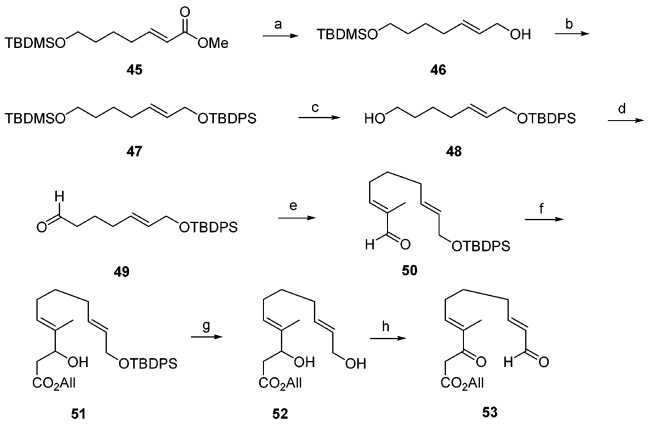
The Nazarov substrate **41** (Scheme 8) and the cyclohexenone **1** underwent the double-Michael cycloaddition, and the sulfoxide was eliminated on silica gel during flash chromatography to afford the tricycle **42** as a mixture of racemic diastereoisomers. The latter, when subjected to a catalytic amount of *p*-TsOH in refluxing benzene, was converted to the racemic tetracyclic products **43** and **44** in 26% yield. The three-dimensional structures were determined by single crystal X-ray diffraction crystallography. These results confirmed that the new carbon−carbon bond is formed on the same side of the chain at C-9 resulting in a *cis* B/C ring junction. Thus it is possible by this approach to obtain the 8β-methyl configuration, which is the one found in most naturally occurring sterols.

We then sought to explore the possibility of making a tricycle in a one-pot sequence using the same methodology. This goal could be achieved with an acyclic Nazarov substrate such as **53** and the cyclohexanone **1**. This sequence would give us the opportunity to employ an α,β-unsaturated aldehyde Michael acceptor, a more activated electrophile that should efficiently trap the in situ formed $\Delta^{7,8}$ enolate resulting from the double-Michael cycloaddition.

The synthesis started from the known α,β-unsaturated ester[26] **45** (Scheme 9), which was reduced with DIBAL-H to the allylic alcohol **46** and then protected as a silyl ether **47**. The TBDMS was selectively removed in acidic EtOH

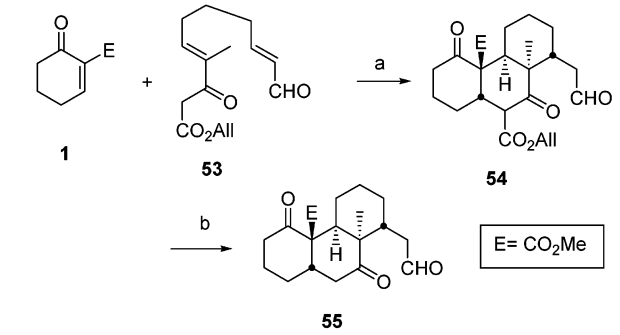
(20) Quesnel, Y.; Bidois-Sery, L.; Poirier, J.-M.; Duhamel, L. *Synlett* **1998**, 413.
(21) Spino, C.; Deslongchamps, P. *Tetrahedron Lett.* **1990**, *31*, 3969.
(22) (a) Conia, J.; M.; Moinet, G. *Bull. Soc. Chim. Fr.* **1990**, 500. (b) Kikani, B. B.; McKee, J. R.; Zanger, M. *Synthesis* **1991**, 176.
(23) Mander, L. N.; Sethi, S. P. *Tetrahedron Lett.* **1983**, *24*, 5425.
(24) Veysoglu, T.; Mitscher, L. A.; Swayze, J. K. *Synthesis* **1980**, 807.
(25) Goldman, S. *Synthesis* **1980**, 640.

SCHEME 9[a]



[a] Reagents and conditions: (a) DIBAL-H, CH_2Cl_2−hexane, 80%; (b) TBDPSCl, imidazole, DMF, 96%; (c) PPTS, EtOH, 85%; (d) Dess−Martin, CH_2Cl_2, 0 °C to rt, 91%; (e) $P(Ph)_3C(Me)CHO$, C_6H_6, reflux, 74%; (f) allyl acetate, LDA, THF, −78 °C, 87%; (g) TBAF, THF, 53%; (h) Dess−Martin, CH_2Cl_2, 72%.

SCHEME 10[a]

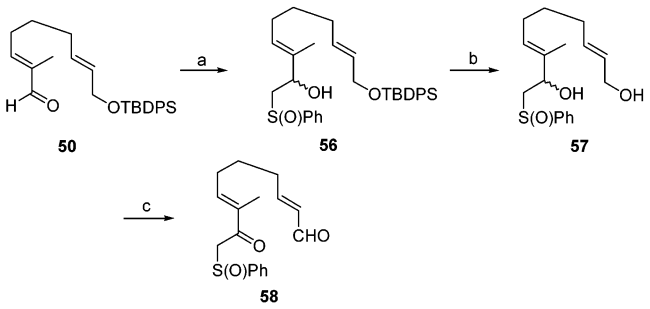


[a] Reagents and conditions: (a) Cs_2CO_3, CH_2Cl_2, 80%; (b) $Pd(PPh_3)_4$, morpholine, THF, 63%.

to yield the alcohol **48**. Further oxidation to the aldehyde **49** using Dess−Martin periodinane and homologation with the stabilized Wittig reagent afforded the α,β-unsaturated aldehyde **50**. Aldol reaction with the enolate of allyl acetate at low temperature furnished the alcohol **51**. The silyl ether was removed with TBAF to yield the diol **52**. Oxidation of the diol with Dess−Martin afforded the Nazarov substrate **53**.

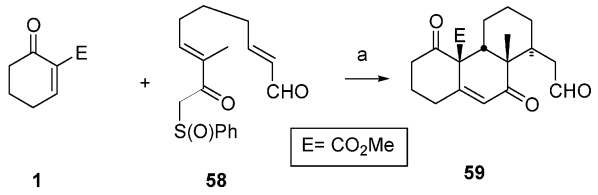
When the Nazarov substrate **53** (Scheme 10) was subjected under basic conditions to the activated cyclohexenone **1**, the double-Michael cycloaddition proceeded and the resulting $\Delta^{7,8}$ enolate was efficiently trapped by the α,β-unsaturated aldehyde to directly provide the tricyclic intermediate **54** in 80% yield. This intermediate was treated with $Pd(PPh_3)_4$ and morpholine, and the dealkoxycarbonylation of the allyl ester proceeded smoothly. The tricycle **55** was isolated in 63% yield, and its three-dimensional structure was ascertained by single-crystal X-ray diffraction analysis. Not too surprisingly, the 8α-methyl and the 14β-hydrogen observed earlier resulted from an attack of the β-face of the $\Delta^{7,8}$ enolate on the α-face of the Michael acceptor.

SCHEME 11[a]



[a] Reagents and conditions: (a) LDA, PhS(O)Me, THF, −78 °C, 77%; (b) TBAF, THF, 88%; (c) Dess−Martin, CH_2Cl_2, 0 °C to rt, 45%.

SCHEME 12[a]



[a] Reagents and conditions: (a) Cs_2CO_3, CH_2Cl_2, 15%.

We then decided to examine the effect of a β-ketosulfoxide Nazarov substrate for the tricycle synthesis. Thus, the Nazarov substrate **58** (Scheme 11) was synthesized starting from aldehyde **50** that was alkylated with methylphenyl sulfoxide anion to yield the alcohol **56**. After desilylation, the diol **57** was further oxidized to the Nazarov substrate **58**. The cyclization with the activated cyclohexenone **1** (Scheme 12) poorly yielded (15%) the tricycle **59** according to spectroscopic analysis.[27]

To finally access the stereochemistry of most natural tricycles, we searched for other factors that could suitably stabilize the transition state leading to the cyclized product. Steric hindrance was regarded at first as one such factor. Thus we surmised that it might be possible to use a 4,4-disubtituted cyclohexenone in order to create enough steric hindrance to force the cyclization to proceed from the α-face of the enolate to yield the 8β-methyl product. To verify this hypothesis, we looked at the cyclization of our previously described Nazarov substrates with the 4,4-dioxolane activated cyclohexenone **60**.[28] The first Nazarov substrate tried was the β-ketosulfoxide **58**. When allowed to cyclize with cyclohexenone **60** (Scheme 13), a surprisingly efficient and specific reaction took place to yield only the tricycle **61** in 48% yield, for which the three-dimensional structure was determined by single-crystal X-ray crystallography.

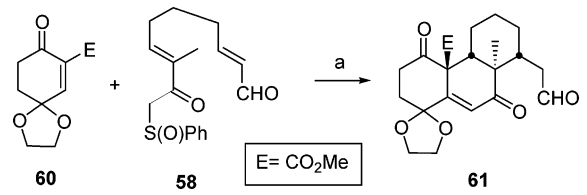
Cyclohexenone **60** is known[28] to be more stable and more reactive than the nonsubstituted one, yielding clean cycloaddition reactions and higher reaction yields. Examination of the possible transition states (Scheme 14) offers a rationale for the observed stereoselectivity. The additional steric hindrance generated between the dioxolane moiety and the B ring in **64** and **65** makes the

(26) Nicolaou, K. C.; Hwang, C.-K.; Marron, B. E.; DeFrees, S. A.; Couladros, E. A.; Abe, Y.; Carroll, P. J.; Snyder, J. P. *J. Am. Chem. Soc.* **1990**, *112*, 3040.

(27) Compound **59** was fully characterized except by single-crystal X-ray diffraction analysis.

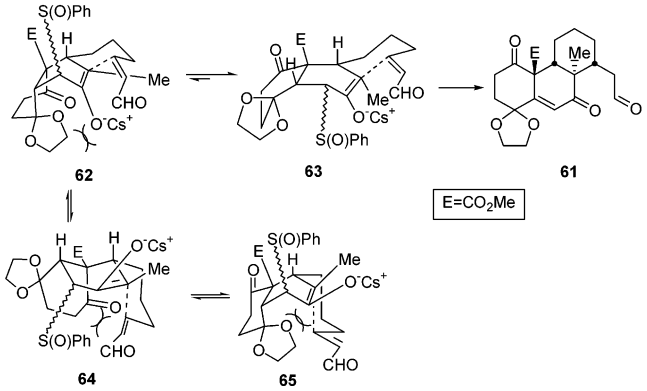
(28) Lavallée, J. F.; Spino, C.; Ruel, R.; Hogan, K.; Deslongchamps, P. *Can. J. Chem.* **1992**, *70*, 1406.

SCHEME 13[a]

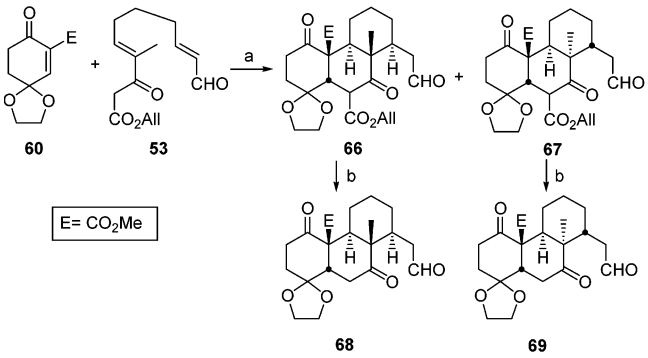


[a] Reagents and conditions: (a) Cs_2CO_3, CH_2Cl_2, 48%.

SCHEME 14



SCHEME 15[a]

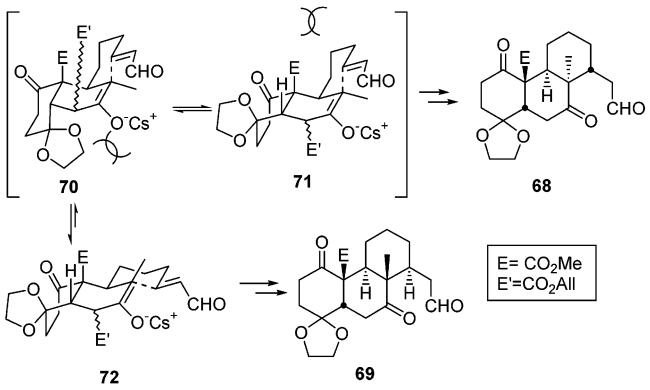


[a] Reagents and conditions: (a) Cs_2CO_3, CH_2Cl_2, 93% of 2.3:1 ratio; (b) $Pd(PPh_3)_4$, morpholine, THF, 67% of **68** and 52% of **69**.

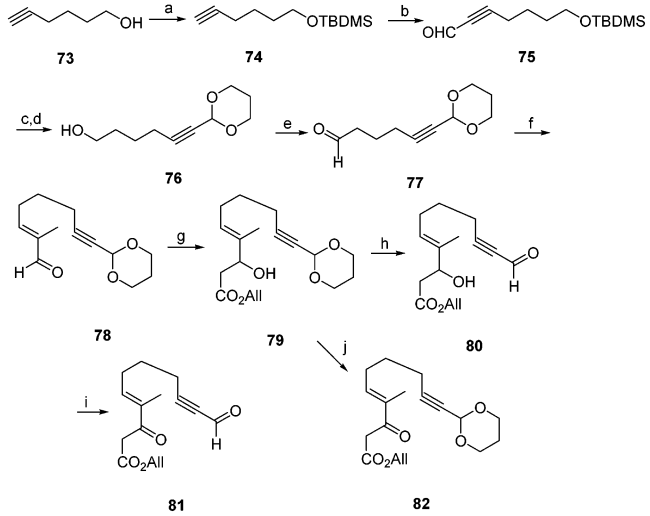
Michael addition sterically impossible from the α-face of the enolate. On the other hand, it allows a conformational change to **62** and then to the more stable conformation **63**, and the attendant cyclization to occur exclusively on the *β*-face to give tricycle **61** with an 8α-methyl and a 9*β*-H.

At this stage of our exploration studies, it was appropriate to try with the *β*-ketoester Nazarov substrate **53** (Scheme 15). This time, the cyclization with the cyclohexenone **60** followed by dealkoxycarbonylation gave a 2.3:1 mixture of inseparable tricycles **68** and **69**. These were obtained pure by separation of the mixture **66** and **67**. Then palladium-catalyzed dealkoxycarbonylation of **66** afforded tricycle **68** in 67% yield, and the same reaction on **67** furnished tricycle **69** in 52% yield. Single-crystal X-ray diffraction analysis was used to corroborate the three-dimensional structures of **68** and **69**. A highly selective reaction was not obtained, but the major product **68** is the one having the stereochemistry at C-8 normally found in sterols. The ratio could probably

SCHEME 16



SCHEME 17[a]



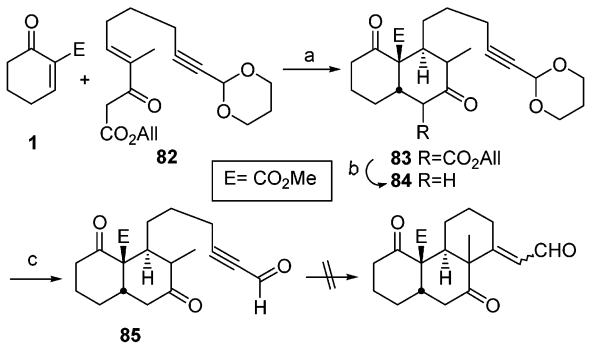
[a] Reagents and conditions: (a) TBDMSCl, imidazole, THF, 98%; (b) *n*-BuLi, DMF, THF, −40 °C to rt, 97%; (c) 1,3-propanediol, PPTS, C_6H_6; (d) TBAF, THF, 0 °C to rt, 80% (2 steps); (e) Dess−Martin, CH_2Cl_2, 0 °C to rt; 70%; (f) $P(Ph)_3C(Me)CHO$, C_6H_6, reflux, 67%; (g) allyl acetate, LDA, THF, −78 °C, 52% (60% corr); (h) *p*-TsOH, H_2O, acetone, reflux, 87%; (i) Dess−Martin, CH_2Cl_2, 68%; (j) Dess−Martin, CH_2Cl_2, 65%.

be increased using a more sterically hindered Nazarov substrate.

Looking at the transition states (Scheme 16) indicates that the two sterically hindered conformations **70** and **71** yielded the minor product, 8α-methyl tricycle **68**. Molecular model examination suggests that conformation **72**, despite less orbital overlapping and while generating ring B in a boat conformation, can lead to the major product **69**. It is clear that in this case, the steric interactions play an important role in the partial reversal of the stereochemistry.

Finally, we looked for a method to make a tricycle with a $\Delta^{14,15}$ olefin that could give access to *trans* C/D ring junction after further reduction or hydrogenation. We imagined a Nazarov substrate with a triple bond conjugated with an aldehyde as the Michael acceptor. The synthesis began by the protection of 5-hexynol **73** with TBDMSCl to yield the protected alcohol **74** in 98% yield (Scheme 17). Lithium anion of the alkyne was acylated with DMF[29] to provide the aldehyde **75** in 97% yield. Protection of the aldehyde and subsequent desilylation yielded the corresponding dioxane-alcohol **76** in 80%

SCHEME 18[a]



[a] Reagents and conditions: (a) Cs_2CO_3, CH_2Cl_2; (b) $Pd(PPh_3)_4$, morpholine, THF, 30% (2 steps); (c) *p*-TsOH, H_2O, acetone, reflux, 45%.

yield. Further oxidation of the alcohol with Dess−Martin periodinane furnished the aldehyde **77** in 70%, and homologation with the stabilized Wittig reagent provided the α,β-unsaturated aldehyde **78**. The aldol reaction with allyl acetate gave the alcohol **79**. The acetal was hydrolyzed with *p*-TsOH in acetone to yield the propargylic aldehyde **80** in 87% yield. Finally, the oxidation of the alcohol furnished the Nazarov substrate **81** in 68% yield.

The cycloaddition of that Nazarov substrate **81** with cyclohexenone **1** led, surprisingly, to a complex mixture of intractable products. To circumvent this shortcoming, we made the reaction stepwise. Oxidation of the alcohol **79** yielded the Nazarov substrate **82** (Scheme 17) in 65% yield, followed by the cyclization with cyclohexenone **1** (Scheme 18) to obtain the bicyclic adduct **83**, which was dealkoxycarbonylated with $Pd(PPh_3)_4$ to afford **84**. The acetal was hydrolyzed with *p*-TsOH in wet acetone to yield the aldehyde **85** in 45% yield. Curiously enough all attempts to cyclize this bicyclic product under mild acidic or basic conditions proved to be unsuccessful, much to our dismay.

Conclusion

In summary, seven new Nazarov substrates were synthesized, and their cyclization with two different activated cyclohexenones yielded tricycles or tetracycles in seven times out of eight, giving a stereoselective access to six different ring junctions.

This exploratory study shows that cascade polycyclization using Michael reaction can become a general method to access tricyclic and tetracyclic intermediates with either natural or unnatural stereochemistry. This methodology permits rapid construction of the polycyclic ring unit and gives access to a wide array of ring junctions. The high degree of convergence makes this methodology a rather powerful one, a fact that was demonstrated herein by making use of cascade polycyclization strategy to obtain a large variety of tricycles and tetracycles. Applications of this attractive method for the total synthesis of naturally occurring steroids and terpenoids are currently underway in our laboratories.

Experimental Section

General Methods. All reactions requiring anhydrous conditions were conducted under a positive atmosphere of nitrogen in flame-dried glassware, using standard syringe techniques. Tetrahydrofuran (THF) and ether were distilled from sodium/benzophenone under N_2 atmosphere immediately prior to use. Methanol was distilled from magnesium/iodine under N_2 atmosphere immediately prior to use. Dichloromethane, diisopropylamine, pyridine, toluene, benzene, and HMPA were freshly distilled from CaH_2 under N_2 atmosphere. DIBAL-H (1 M solution in dichloromethane) was used. *n*-BuLi (1.6 M solution in hexane) was titrated according to literature.[30] Sodium and potassium hydrides were washed under nitrogen with hexane prior to use. Methyl cyanoformate and methylphenyl sulfoxide were distilled prior to use. Activated zinc was prepared by washing granular zinc successively with 1 M hydrochloric acid, water, methanol, and then ether, immediately before use in Reformatsky reactions. Drying of organic extracts were performed with anhydrous magnesium sulfate. Flash chromatography was performed on Merck silica gel 60 (or Silicycle equivalent recycled product) using air pressure according to literature's procedure.[31] Analytical thin-layer chromatography (TLC) was carried out on precoated (0.25 mm) Merck silica gel 60f-254 plates. Detection of spots was done by visualization under UV lamp and further treatment with an aqueous revealing solution (sulfuric acid−molybdic acid, cerium ammonium nitrate, or potassium permanganate−potassium carbonate) and heating. Melting points were determined on a Büchi M-50 melting point apparatus and were uncorrected. X-ray diffraction crystallographic analyses were performed on a monocrystal of pure recrystallized compound.

Tetracycle 17 and Tetracycle 18. To a stirred suspension of cesium carbonate (24 mg, 0.08 mmol) and β-ketoester **15** (15 mg, 0.05 mmol) in CH_2Cl_2 (1 mL) was rapidly added a solution of cyclohexenone **1** (15 mg, 0.10 mmol) in CH_2Cl_2 (1 mL). The suspension was stirred for 5 h, filtered on a silica gel pad, and washed with EtOAc−hexane (50:50). The filtrate was concentrated under vacuum, and the residue was purified by flash chromatography using EtOAc−hexane (40:60) to yield the tricycle **16** (mixture of diastereoisomers) as a clear oil. The tricycle was used without additionnal purification in the next step. To a stirred solution of the tricyclic *tert*-butyl-β-ketoester **16** (23 mg, 0.05 mmol) in benzene (1.5 mL) was added *p*-TsOH (1 mg, 0.005 mmol). The reaction mixture was refluxed for 2 h 30 min and then cooled to room temperature. The mixture was filtered on a silica gel pad washed with EtOAc−hexane (40:60), after which the filtrate was concentrated under vacuum. The residue was purified by flash chromatography using EtOAc−hexane (40:60) to yield tetracycles **17** (7 mg, 40%) and **18** (7 mg, 40%) as white crystalline solids. Spectral data for **17**. Molecular formula: $C_{21}H_{28}O_5$. Melting point: 173−174 °C. IR (film, ν cm^{-1}): 1739, 1716. ^1H NMR(300 MHz, $CDCl_3$, δ ppm): 3.72 (s, 3H), 3.28−3.38 (m, 1H); 3.06−3.10 (m, 1H); 2.92 (dd, 1H, J = 9.5 Hz, J = 11.5 Hz); 2.73 (dd, 1H, J = 4.2 Hz, J = 16.7 Hz); 2.58 (dddd, 1H, J = 3.5 Hz, J = 5.5 Hz, J = 8.5 Hz, J = 15.5 Hz); 2.17−2.44 (m, 6H); 2.07 (d, 1H, J = 17.2 Hz); 1.88−1.98 (m, 2H); 1.51−1.61 (m, 1H); 1.20−1.41 (m, 4H); 1.05 (s, 3H); 0.99 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 216.9, 212.1, 204.9, 170.2, 64.2, 56.0, 53.3, 50.6, 45.1, 40.8, 40.1, 39.8, 38.6, 38.0, 35.3, 32.9, 29.5, 27.2, 25.6, 23.8, 19.8. MS (*m*/*e*): 360 (M^+). HRMS: (M^+) calcd 360.1937, found 360.1939 ± 0.0011. Spectral data for **18**. Molecular formula: $C_{21}H_{28}O_5$. Melting point: 171−172 °C. IR (film, ν cm^{-1}): 1739, 1712. ^1H NMR(300 MHz, $CDCl_3$, δ ppm): 3.73 (s, 3H), 3.21−3.30 (m, 1H); 3.01 (dd, 1H, J = 2.4 Hz, J = 12.1 Hz); 2.76 (t, 1H, J = 14.3 Hz); 2.63 (dddd, 1H, J = 2.4 Hz, J = 5.5 Hz, J = 8.5 Hz, J = 15.9 Hz); 2.42 (d, 2H, J = 20.3 Hz); 2.20−2.37 (m, 2H); 2.01 (dd, 1H, J = 5.9 Hz, J = 14.4 Hz); 1.89−1.97 (m, 3H); 1.69 (d, 1H, J = 17.5 Hz); 1.51−1.58 (m, 1H); 1.46 (td,

(29) Journet, M.; Cai, D.; DiMichele, L. M.; Larsen, R. D. *Tetrahedron Lett.* **1998**, *39*, 6427.

(30) Bergbreiter, D. E.; Pendergrass, E. *J. Org. Chem.* **1981**, *46*, 219.
(31) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.*, **1978**, *43*, 2923.

2H, J = 4.1 Hz, J = 13.9 Hz); 1.18 (s, 3H); 1.06 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 218.0, 213.7, 205.2, 170.0, 64.8, 53.4, 53.2, 52.2, 48.3, 47.5, 41.5, 41.0, 38.3, 37.8, 35.7, 32.4, 29.7, 28.8, 27.4, 23.0, 19.7. MS (*m*/*e*): 360 (M^+). HRMS: (M^+) calcd 360.1937, found 360.1939 ± 0.0011.

Tetracycle 29. The cyclization was done according to the procedure already described for tetracycles **17** and **18**. The crude material was purified by flash chromatography using EtOAc−hexane (40:60) to yield the tricycle **28** (mixture of diastereoisomers) as a yellow oil. The product was used for next step without further purification. To a stirred solution of tricyclic *tert*-butyl-β-ketoester **28** (45 mg, 0.1 mmol) in benzene (3 mL) was added *p*-TsOH (2 mg, 0.01 mmol). The reaction mixture was refluxed for 10 h and then cooled to room temperature. The mixture was filtered on a silica gel pad washed with EtOAc−hexane (50:50) after which the filtrate was concentrated under vacuum. The residue was purified by flash chromatography using EtOAc−hexane (50:50) to yield tetracycle **29** (18 mg, 50% (2 steps)) (mixture of epimers) as a colorless oil and the dealkoxycarbonylated tricycle **30** (6 mg, 20% (2 steps)) as a colorless oil. Spectral data for **29** (mixture of epimers). Molecular formula: $C_{20}H_{26}O_5$. ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 3.81 (s, 3H), (diast. 3.79); 3.18 (dd, 2H, J = 6.2 Hz, J = 13.1 Hz); 2.53−3.10 (m, 4H); 2.08−2.50 (m, 7H); 1.33−2.02 (m, 5H); 1.18−1.30 (m, 2H); 1.22 (s, 3H), (diast. 1.05). Spectral data for **30**. Molecular formula: $C_{20}H_{26}O_5$. ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 7.34 (d, 1H, J = 5.6 Hz); 6.02 (d, 1H, J = 5.6 Hz); 3.73 (s, 3H), 3.04−3.13 (m, 1H); 2.00−2.78 (m, 10H); 2.12 (d, 2H, J = 6.5 Hz); 1.20−1.96 (m, 5H); 1.18 (s, 3H).

Tetracycle 31. To a stirred solution of tricycle **30** (6 mg, 0.02 mmol) in toluene (2 mL) was added *p*-TsOH (0.5 mg, 0.002 mmol). The reaction mixture was refluxed for 2 h and then cooled to room temperature. The mixture was filtered on a silica gel pad washed with EtOAc−hexane (50:50) after which the filtrate was concentrated under vacuum. The residue was purified by flash chromatography using EtOAc−hexane (50:50) to yield tetracycle **31** (6 mg, 100%) as a white crystalline solid. Molecular formula: $C_{20}H_{26}O_5$. Melting point: 167−168 °C. IR (film, ν cm^{-1}): 1737, 1706. ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 3.79 (s, 3H), 3.06−3.14 (m, 1H); 2.77 (dd, 1H, J = 7.5 Hz, J = 19.6 Hz); 2.66 (d, 1H, J = 11.3 Hz); 1.96−2.51 (m, 8H); 1.56−1.92 (m, 7H); 1.23−1.33 (m, 2H); 1.08 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 219.2, 208.7, 207.3, 171.3, 65.7, 52.4, 51.5, 46.5, 45.3, 45.0, 42.8, 41.6, 41.1, 38.3, 38.0, 34.8, 29.5, 26.3, 24.4, 21.6. MS (*m*/*e*): 346 (M^+). HRMS: (M^+) calcd 346.1780, found 346.1776 ± 0.0010.

Tetracycle 43 and Tetracycle 44. To a stirred suspension of Cs_2CO_3 (45 mg, 0.14 mmol) and β-ketosulfoxide **41** (45 mg, 0.14 mmol) in CH_2Cl_2 (2 mL) was added a solution of cyclohexenone **1** (85 mg, 0.54 mmol) in CH_2Cl_2 (3 mL) at a rhythm of 1 equiv (1 mL, 0.18 mmol) first and the remaining material dropwise over 3 h using a syringe pump. After addition completed, the mixture was stirred for 3 h then filtered on a silica gel pad, washed with EtOAc. The filtrate was concentrated under vacuum, and the residual β-ketosulfoxide **41** was removed by flash chromatography using EtOAc to yield the crude tricycle **42** (55 mg) as a yellow oil. The product was used for next step without further purification. To a stirred solution of tricycle **42** (55 mg, 0.15 mmol) in benzene (5 mL) was added *p*-TsOH (6.0 mg, 0.03 mmol). The reaction mixture was refluxed for 2 h and then cooled to room temperature. The mixture was filtered on a silica gel pad washed with EtOAc−hexane (50:50) after which the filtrate was concentrated under vacuum. The residue was purified by flash chromatography using EtOAc−hexane (50:50) to yield tetracycles **43** (3 mg, 13% (2 steps)) and **44** (3 mg, 13% (2 steps)) as white crystalline solids. Spectral data for **43**. Molecular formula: $C_{21}H_{26}O_5$. Melting point: 161−163 °C. IR (film, ν cm^{-1}): 1740, 1715, 1667, 1629. ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 6.09 (d, 1H, J = 1.6 Hz); 3.74 (s, 3H); 3.03−3.16 (m, 2H); 2.97 (d, 1H, J = 8.3 Hz); 2.72 (dt, 1H, J = 4.4 Hz, J = 15.5 Hz); 2.55 (t, 1H, J = 5.0 Hz); 2.31 (d, 2H, J = 10.1 Hz); 2.03−2.26 (m, 2H); 1.64−1.93 (m, 1H); 1.20−1.54 (m, 5H); 0.95 (s, 3H); 0.89 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 216.6, 203.3, 199.7, 168.8, 155.7, 126.0, 67.0, 55.7, 53.7, 47.2, 46.3, 43.3, 40.6, 38.9, 38.2, 33.2, 32.5, 25.7, 24.6, 22.5, 20.2. MS (*m*/*e*): 358 (M^+). HRMS: (M^+) calcd 358.1780, found 358.1783 ± 0.0011. Spectral data for **44**. Molecular formula: $C_{21}H_{26}O_5$. Melting point: 181−182 °C. IR (film, ν cm^{-1}): 1747, 1732, 1714, 1674. ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 5.86 (d, 1H, J = 1.8 Hz); 3.77 (s, 3H); 3.05−3.17 (m, 1H); 2.91−2.99 (m, 2H); 2.63 (dt, 1H, J = 4.4 Hz, J = 15.3 Hz); 2.54 (t, 2H, J = 5.0 Hz); 2.44−2.51 (m, 1H); 2.19 (d, 1H, J = 17.6 Hz); 2.03−2.14 (m, 1H); 1.82 (d, 1H, J = 9.6 Hz); 1.46−1.78 (m, 5H); 1.14−1.24 (m, 1H); 1.06 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 217.9, 203.4, 202.1, 169.1, 153.9, 127.4, 68.4, 53.7, 53.0, 49.3, 48.9, 48.2, 40.9, 40.4, 39.0, 35.3, 32.7, 31.6, 23.6, 23.0, 20.4. MS (*m*/*e*): 358 (M^+). HRMS: (M^+) calcd 358.1780, found 358.1783 ± 0.0011.

Tricycle 55. To a stirred suspension of Cs_2CO_3 (44 mg, 0.13 mmol) and allylic β-ketoester **53** (35 mg, 0.13 mmol) in CH_2Cl_2 (1 mL) was added a solution of cyclohexenone **1** (82 mg, 0.53 mmol) in CH_2Cl_2 (2 mL) at a rhythm of 1 equiv (0.5 mL, 0.13 mmol) first and the remaining material dropwise over 3 h using a syringe pump. After addition completed, the mixture was stirred for 3 h and filtered on a silica gel pad, washed with EtOAc−hexane (50:50). The filtrate was concentrated under vacuum, and the crude material was purified by flash chromatography using EtOAc−hexane (50:50) to yield the tricyclic β-ketoester **54** (44 mg, 80%) as a yellow oil. The product was used for next step without further purification. To a stirred solution of tricyclic β-ketoester **54** (44 mg, 0.11 mmol) in THF (1 mL) were added morpholine (42 μL, 0.50 mmol) and palladium tetrakis(triphenylphosphine) (3 mg, 0.002 mmol). The mixture was stirred for 2 h 30 min and filtered on a silica gel pad, washed with EtOAc−hexane (50:50). The filtrate was concentrated under vacuum, and the crude material was purified by flash chromatography using EtOAc−hexane (50:50) to yield tricycle **55** (10 mg, 63%) as a white crystalline solid. Molecular formula: $C_{19}H_{26}O_5$. Melting point: 116−118 °C. IR (film, ν cm^{-1}): 1714. ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 9.70 (dd, 1H, J = 1.0 Hz, J = 2.6 Hz); 3.73 (s, 3H); 3.36−3.50 (m, 1H); 3.00 (dd, 1H, J = 5.5 Hz, J = 9.4 Hz); 2.73−2.82 (m, 1H); 2.51−2.62 (m, 3H); 2.16−2.39 (m, 4H); 1.89−1.96 (m, 2H); 1.40−1.71 (m, 4H); 1.18−1.38 (m, 3H); 1.03 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 212.9, 205.4, 201.9, 170.4, 64.1, 53.1, 50.8, 44.1, 40.9, 40.7, 39.2, 35.7, 32.7, 27.2, 26.8, 24.9, 20.4, 20.3. MS (*m*/*e*): 334 (M^+). HRMS: (M^+) calcd 334.1780, found 334.1775 ± 0.0010.

Tricycle 59. To a stirred suspension of Cs_2CO_3 (64 mg, 0.20 mmol) and β-ketosulfoxide **58** (60 mg, 0.20 mmol) in CH_2Cl_2 (2 mL) was added a solution of cyclohexenone **1** (120 mg, 0.77 mmol) in CH_2Cl_2 (2 mL) at a rhythm of 1 equiv (0.5 mL, 0.20 mmol) first and the remaining material dropwise over 3 h using a syringe pump. After addition completed, the mixture was stirred for 3 h and filtered on a silica gel pad, washed with EtOAc. The filtrate was concentrated under vacuum, and the crude material was purified by flash chromatography using EtOAc−hexane (50:50) to yield the tricycle **59** (5 mg, 15%) as a yellow oil. Molecular formula: $C_{19}H_{24}O_5$. IR (film, ν cm^{-1}): 1738, 1720, 1670. ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 9.78 (d, 1H, J = 2.5 Hz); 5.69 (d, 1H, J = 1.6 Hz); 3.80 (s, 3H); 3.36 (dd, 1H, J = 16.7 Hz, J = 2.3 Hz); 2.26−2.71 (m, 6H); 1.99−2.10 (m, 2H); 1.51−1.78 (m, 4H); 1.11−1.31 (m, 3H); 0.97 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 203.8, 202.8, 202.4, 171.4, 154.0, 125.9, 67.0, 53.4, 49.0, 48.3, 46.2, 41.0, 36.1, 33.1, 30.2, 26.5, 23.9, 23.1, 15.0. MS (*m*/*e*): 332 (M^+). HRMS: (M^+) calcd 332.1624, found 332.1631 ± 0.0010.

Tricycle 61. To a stirred suspension of Cs_2CO_3 (73 mg, 0.22 mmol) and β-ketosulfoxide **58** (68 mg, 0.22 mmol) in CH_2Cl_2 (2 mL) was added a solution of cyclohexenone **60** (57 mg, 0.27 mmol) in CH_2Cl_2 (2 mL). The mixture was stirred for 3 h and then filtered on a silica gel pad, washed with EtOAc−hexane (50:50). The filtrate was concentrated under vacuum, and the

crude material was purified by flash chromatography using EtOAc−hexane (50:50) to yield the tricycle **61** (40 mg, 48%) as a white crystalline solid. Molecular formula: $C_{21}H_{26}O_7$. Melting point: 150−151 °C. IR (film, ν cm^{-1}): 1738, 1731, 1682. ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 9.75 (t, 1H, J = 1.4 Hz); 6.19 (d 1H, J = 1.2 Hz); 3.95−4.10 (m, 3H); 3.73 (s, 3H); 3.66−3.78 (m, 1H); 3.21 (dd, 1H, J = 0.8 Hz, J = 15.2 Hz); 3.19 (ddd, 1H, J = 0.8 Hz, J = 7.1 Hz, J = 14.3); 2.47−2.62 (m, 2H); 1.89−2.12 (m, 3H); 1.68−1.72 (m, 1H); 1.53−1.57 (m, 1H); 1.38−1.44 (m, 1H); 1.08−1.25 (m, 2H); 0.90 (d, 3H, J = 0.8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 204.0, 202.2, 202.1, 171.1, 150.4, 125.0, 106.2, 65.5, 64.5, 64.2, 53.1, 49.6, 48.1, 46.4, 38.6, 35.9, 33.8, 30.0, 26.5, 23.8, 14.6. MS (*m*/*e*): 390 (M^+). HRMS: (M^+) calcd 390.1678, found 390.1686 ± 0.0011.

Tricycles 66 and 67. To a stirred suspension of Cs_2CO_3 (96 mg, 0.30 mmol) and allylic β-ketoester **53** (78 mg, 0.30 mmol) in CH_2Cl_2 (3 mL) was added a solution of cyclohexenone **60** (81 mg, 0.38 mmol) in CH_2Cl_2 (3 mL). The mixture was stirred for 3 h and then filtered on a silica gel pad, washed with EtOAc−hexane (50:50). The filtrate was concentrated under vacuum, and the crude material was purified by flash chromatography using EtOAc−hexane (50:50) to yield the tricyclic β-ketoesters **66** and **67** (130 mg, 93%) (ratio 2.3:1 favoring **66**). The products were separated by flash chromatography with 50% EtOAc−hexane to yield **66** and **67** as keto enol mixtures. These were used for next step without characterization.

Tricycle 68. To a stirred solution of tricyclic β-ketoester **66** (4 mg, 0.01 mmol) in THF (1 mL) were added morpholine (7 μL, 0.10 mmol) and tetrakis(triphenylphosphine) palladium (1 mg, 0.001 mmol). The mixture was stirred for 2 h and then filtered on a silica gel pad, washed with EtOAc−hexane (50:50). The filtrate was concentrated under vacuum, and the crude material was purified by flash chromatography using EtOAc−hexane (50:50) to yield the tricycle **68** (2.2 mg, 67%) as a white crystalline solid. Melting point: 137−138 °C. IR (film, ν cm^{-1}): 1715, 1449. ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 9.75 (d, 1H, J = 2.2 Hz); 3.93−4.04 (m, 4H); 3.79 (s, 3H); 3.36 (dd, 1H, J = 3.0 Hz, J = 17.1 Hz); 3.25 (dd, 1H, J = 5.1 Hz, J = 7.1 Hz); 2.94 (dd, 1H, J = 2.2 Hz, J = 12.0 Hz); 2.55−2.74 (m, 3H); 2.22−2.35 (m, 2H); 1.86−2.11 (m, 3H); 1.58−1.77 (m, 2H), 1.16−1.43 (m, 4H); 1.07 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 213.6, 206.9, 202.2, 171.7, 107.8, 65.3, 64.6, 63.2, 52.2, 49.5, 47.9, 46.5, 45.4, 37.2, 36.4, 33.4, 30.1, 29.7, 26.4, 24.7, 13.5. MS (*m*/*e*): 392 (M^+). HRMS: (M^+) calcd 392.1844, found 392.1844 ± 0.0011.

Tricycle 69. To a stirred solution of tricyclic β-ketoester **67** (7 mg, 0.01 mmol) in THF (1 mL) were added morpholine (13 μL, 0.10 mmol) and tetrakis(triphenylphosphine) palladium (2 mg, 0.002 mmol). The mixture was stirred for 2 h and then filtered on a silica gel pad, washed with EtOAc−hexane (50:50). The filtrate was concentrated under vacuum, and the crude material was purified by flash chromatography using EtOAc−hexane (50:50) to yield the tricycle **69** (3 mg, 52%) as a white crystalline solid. Molecular formula: $C_{21}H_{28}O_7$. Melting point: 150−151 °C. IR (film, ν cm^{-1}): 1741, 1714, 1644. ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 9.66 (d, 1H, J = 1.1 Hz); 3.95−4.14 (m, 4H); 3.78 (s, 3H); 3.62 (ddd, 1H, J = 1.9 Hz, J = 4.9 Hz, J = 11.6 Hz); 2.80−2.94 (m, 4H); 2.50−2.62 (m, 3H); 2.05−2.24 (m, 3H); 1.87−1.96 (m, 1H); 1.60−1.72 (m, 1H), 1.22−1.54 (m, 4H); 1.06 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 213.6, 205.7, 201.8, 171.6, 107.5, 64.9, 64.0, 61.7, 52.9, 49.6, 45.7, 41.8, 40.8, 37.1, 36.9, 31.4, 30.9, 27.0, 23.0, 20.4, 19.8. MS (*m*/*e*): 392 (M^+). HRMS: (M^+) calcd 392.1835, found 392.1832 ± 0.0011.

Tricycle 84. To a stirred suspension of Cs_2CO_3 (105 mg, 0.33 mmol) and allylic β-ketoester **82** (105 mg, 0.33 mmol) in CH_2Cl_2 (2 mL) was added a solution of cyclohexenone **1** (150 mg, 1.0 mmol) in CH_2Cl_2 (3 mL) at a rhythm of 1 equiv (1 mL, 0.33 mmol) first and the remaining material dropwise over 3 h using a syringe pump. After addition completed, the mixture was stirred for 3 h and then filtered on a silica gel pad, washed with EtOAc−hexane (50:50). The filtrate was concentrated under vacuum, and the crude material was purified by flash chromatography using EtOAc−hexane (50:50) to yield the decalinic β-ketoester **83** (155 mg) as a yellow oil. The product was used for next step without further purification. To a stirred solution of bicyclic β-ketoester **83** (155 mg, 0.32 mmol) in THF (2 mL) were added morpholine (83 μL, 0.95 mmol) and palladium tetrakis(triphenylphosphine) (37 mg, 0.03 mmol). The mixture was concentrated under vacuum, and the crude material was purified by flash chromatography using EtOAc−hexane (30:70) to yield the decaline **84** (37 mg, 30% (2 steps)) as a clear oil. Molecular formula: $C_{22}H_{30}O_6$. IR (film, ν cm^{-1}): 2249, 1740, 1714, 1654. ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 5.29 (d, 2H, J = 0.7 Hz); 4.13 (dt, 2H, J = 4.5 Hz, J = 11.9 Hz); 3.73−3.83 (m, 2H); 3.71 (s, 3H); 3.08−3.18 (m, 1H); 2.98 (quint, 1H, J = 6.5 Hz); 1.10−2.64 (m, 17H); 0.99 (d, 3H, J = 6.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 211.4, 206.1, 170.1, 90.7, 85.8, 75.8, 65.3, 64.5, 52.8, 44.9, 44.8, 42.7, 41.0, 39.9, 29.4, 26.9, 25.6, 24.7, 21.9, 18.6, 11.7. MS (*m*/*e*): 390 (M^+). HRMS: (M^+) calcd 390.2042, found 390.2029 ± 0.0011.

Tricycle 85. To a stirred solution of acetal **84** (28 mg, 0.07 mmol) in acetone (5 mL) were added water (250 μL) and *p*-TsOH (3 mg, 0.01 mmol). The mixture was refluxed for 36 h and then cooled to room temperature. The mixture was diluted with EtOAc and water and concentrated under vacuum. The residue was diluted with EtOAc, the mixture was decanted, and the aqueous phase was extracted with EtOAc. The combined organic phases were washed with brine, dried, and concentrated under vacuum. The crude material was purified by flash chromatography using EtOAc−hexane (50:50) to yield the propargylic aldehyde **85** (10 mg, 45%) as a clear oil. Molecular formula: $C_{19}H_{24}O_5$. IR (film, ν cm^{-1}): 2200, 1739, 1714, 1667, 1652. ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 9.17 (t, 1H, J = 0.7 Hz); 3.75 (s, 3H); 3.13−3.19 (m, 1H); 3.04 (quint, 1H, J = 5.5 Hz); 2.67 (q, 1H, J = 4,6 Hz); 2.13 (m, 6H); 1.89−1.99 (m, 2H); 1.12−1.80 (m, 6H); 1.03 (d, 3H, J = 6.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 211.3, 206.0, 177.1, 170.1, 97.8, 81.9, 64.4, 52.8, 45.0, 44.8, 42.7, 41.0, 40.0, 28.6, 26.9, 24.7, 21.9, 19.2, 11.7. MS (*m*/*e*): 332 (M^+), 317 ($M^+ - CH_3$), 303 ($M^+ - CHO$), 301 ($M^+ - OCH_3$). HRMS: (M^+) calcd 332.1624, found 332.1635 ± 0.0010; ($M^+ - CH_3$) calcd 317.1389, found 317.1396 ± 0.0009.

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Supporting Information Available: Experimental procedures and characterization data for all new compounds, ^{1}H NMR spectra for all compounds, and X-ray crystal structure data for compounds **17**, **18**, **31**, **43**, **44**, **55**, **61**, **68** and **69** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org. The following crystal structures have been deposited at the Cambridge Crystallographic Data Centre: **17** (CCDC 197359), **18** (CCDC 197360), **31** (CCDC 197361), **43** (CCDC 197362), **44** (CCDC 197363), **55** (CCDC 197364), **61** (CCDC 197365), **68** (CCDC 197366), and **69** (CCDC 197367).

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