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Stereoselective Synthesis of Bicyclo[4.2.1]nonanes – a Temporary-Bridge Approach to Cyclooctanoids

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A series of *cis*-α,γ-difunctionalized five-membered cyclic β-oxo esters have been chemo-, regio- and diastereoselectively prepared through an efficient domino anionic ring-cleavage/ring-reconstitution/alkylation sequence including a 1,3-shift of the ester group. These unsaturated substrates were successfully engaged in various ring-closing metatheses to provide a reliable access to functionalized bicyclo[4.2.1]nonanes, precursors of cyclooctanoids following the selective fragmentation of the one-carbon bridge.

Introduction

Cyclooctanoids are often encountered in naturally occurring secondary metabolites and bioactive compounds and have thus attracted considerable attention from the synthetic community.[1] The synthesis of medium-sized rings, and in particular eight-membered rings, by conventional cyclization approaches can hardly be realized efficiently due to both disfavoring entropic and enthalpic factors. An arsenal of original alternative strategies, mostly based on conformational control, have been elaborated over the years for the specific construction of these highly valuable compounds. Among these, the temporary-bridge approach involving the selective formation and subsequent fragmentation of a bridged intermediate is a particularly attractive concept. Both hetero-bridged[2] and carbon-bridged[3] intermediates have been successfully used for the synthesis of seven- to nine-membered rings. In the context of cyclooctanoid synthesis, three types of bridged precursors can be envisioned: the [3.3.*n*], [4.2.*n*], and [5.1.*n*] bicyclic systems ($n \geq 1$). Following the pioneering work of Buchanan and co-workers on the fragmentation of bicyclo[3.3.1]nonane systems,[4] several groups have successfully applied this strategy for the construction of cyclooctanoids.[5] The fragmentation of a bicyclo[5.1.1]nonane has been reported in an isolated example.[6] Several synthetic approaches to cyclooctanoids related to the present study have been realized from a properly functionalized bicyclo[4.2.1]nonane intermediate. The selective cleavage of the one-carbon bridge of a bicyclo[4.2.1]nonane derivative, first observed by Carruthers in 1973,[7] was not further developed until recently because of the lack of general access to functionalized bicyclo[4.2.1] skeletons.[8] Some years ago, we used this temporary-bridge approach for the facile one-pot preparation of functionalized cyclooctenes using the selective formation and retro-Dieckmann fragmentation of bridged bicyclo[4.2.1]nonan-9-ones.[9] Following this work, Zhang and co-workers reported an example of an interesting intramolecular diazo ketone insertion followed by a Grob-type fragmentation to the corresponding eight-membered ring.[8d] During the same period, the group of Mascareñas disclosed a rapid and versatile approach based on ring-closing metathesis and subsequent $Pb(OAc)_4$-promoted ring cleavage of bridgehead-hydroxybicyclo[4.2.1]nonan-9-ones.[10] In connection with our research program on the development of efficient synthetic routes to bridged bicyclic compounds and their applications in organic synthesis, we report herein the full account of our recent results on the chemo-, regio-, and stereocontrolled preparation of a variety of substituted bicyclo[4.2.1]nonan-9-ones and briefly demonstrate their synthetic value through a series of subsequent transformations.[11]

Results and Discussion

Syntheses of the Unsaturated Precursors

The planned strategy for the regio- and stereocontrolled rapid construction of bicyclo[4.2.1]nonan-9-ones is high-

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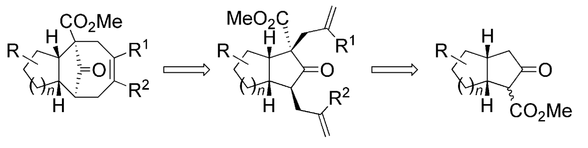
lighted in Scheme 1. The desired bridged bicyclic product would result from a metal-catalyzed cyclization of a diunsaturated precursor, which must exhibit a 1,3-*cis* relationship between the two unsaturated substituents for the cyclization to be possible. To ensure the installation of the two allyl chains in the required configuration, we envisioned taking advantage of the stereocontrol offered by a *cis*-fused bicyclo[x.3.0] system.

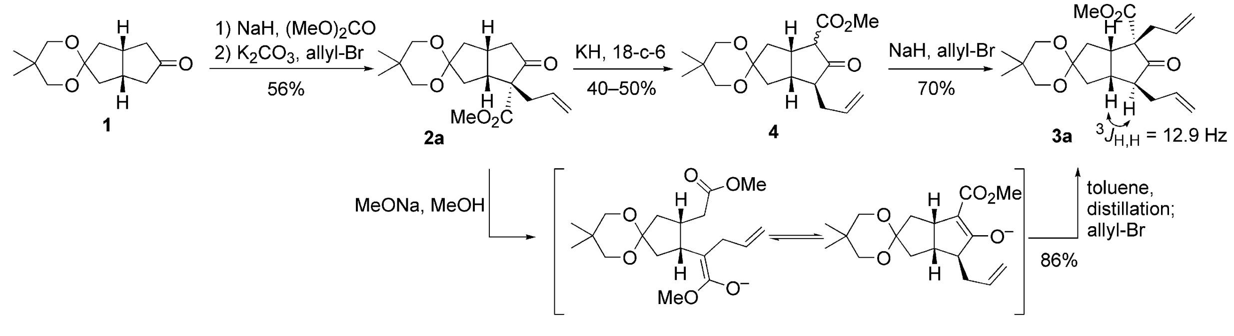


Scheme 1.

We initiated the study with the easily accessible monoprotected bicyclo[3.3.0]octanone **1**,[12] which was efficiently α-carbonylated[13] and then stereoselectively α-alkylated[14] without difficulty to provide β-oxo ester **2a**.[15] The second alkylation in the γ-position required considerable study to be resolved satisfactorily. Indeed, we rapidly realized that the γ-alkylation of **2a** through the reaction of its lithium enolate or enamine with allyl bromide was problematic, resulting in poor yields of the α,γ-diallylated product **3a**. In order to achieve a better activation of the γ-position for the second alkylation to proceed efficiently, we turned our attention to the 1,3-shift of the ester group through a putative cyclobutanone intermediate proposed by Gravel in 1994.[16] Thus, according to the conditions developed by Gravel, treatment of **2a** with potassium hydride in the presence of 5 equiv. of 18-crown-6 ether afforded rearranged β-oxo ester **4** in 40–50% yield (Scheme 2). At this stage, the determination of the configuration of the allyl substituent in **4** was complicated by the existence of the product as two diastereomers at the epimerizable center. However, some semi-empirical calculations performed on the enol form of **4** showed that the desired product with the allyl substituent on the β-face was thermodynamically favored.[17] From **4**, the second allylation could be performed in 70% yield with sodium hydride and allyl bromide to give the desired diallylated product **3a** showing the required 1,3-*cis* relationship between the two unsaturated substituents. The stereochemical assignment followed from the large ${}^3J_{\mathrm{H,H}}$ coupling constant (12.9 Hz) observed between the proton at the new γ-position and the bridgehead proton, indicating a *trans* relationship, which was later confirmed by X-ray diffraction analysis on a direct analog of **3a** (**3c**).[15]

Although this methodology allowed us to prepare the desired substrate, it was not efficient enough and too expensive on a preparative scale due to the use of a large excess of the crown ether. We then looked for an alternative protocol for the 1,3-ester shift in **2a** involving a retro-Dieckmann fragmentation/Dieckmann cyclization as described by Isida and co-workers.[18] It is of importance that the coupling of the 1,3-shift of the ester group with the direct alkylation of the resulting enolate was later proven possible by Dauben and co-workers in their synthesis of fenestranes[19a] and by Paquette and co-workers in their related work on triquinane synthesis.[19b] Thus, we found that the desired synthesis of **3a** could be realized very efficiently from **2a** by using a domino, anionic, ring-cleavage/ring-reconstitution/alkylation sequence including a 1,3-shift of the ester group (Scheme 2). Treatment of **2a** for 1 h with sodium methoxide in refluxing methanol provided the transient shifted ester enolate, which, after removal of methanol by azeotropic distillation with toluene, was allowed to react with allyl bromide to furnish stereoselectively the desired 1,3-*cis*-diallylated product **3a** as the only detectable isomer. The method proved to be very general and was applied successfully to the preparation of a number of analogs of **3a** (Table 1). The regioisomeric monoprotected bicyclo[3.3.0]-octanone **2e** could be transformed into the diallyl product **3k** according to the same methodology. Overall, the method allows for a total regiocontrol of the preparation of unsymmetrical products with excellent stereocontrol (compare, for example, the regioisomeric products **3b** with **3h**, and **3d** with **3i**). We also prepared two substrates with an sp^3-hybridized carbon bridge atom. The treatment of **3a** with $LiAlH_4$ yielded an inseparable 4:1 mixture of **5a** epimers (wherein the major epimer was β-OH), while the partial reduction of **3b** with $NaBH_4$ in methanol yielded a separable 4:1 mixture of **5b** epimers (wherein the major epimer was α-OH, see Table 2).[20]

Another series of substrates was prepared from cyclohexene through a synthetic sequence consisting of a [2+2] cycloaddition of dichloroketene,[21a] dechlorination,[21b] and regio- and stereoselective alkylation at the ring junction[22]



Scheme 2.

Table 1. Domino, ring-cleavage/ring-reconstitution/alkylation sequence.

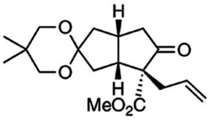
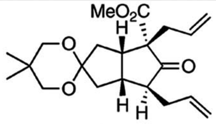
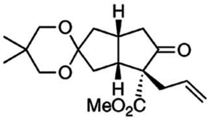
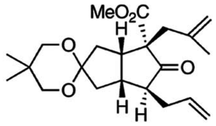
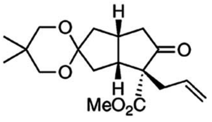
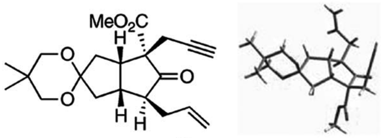
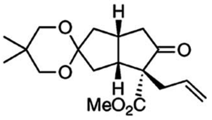
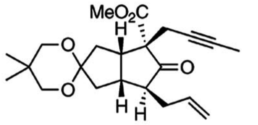
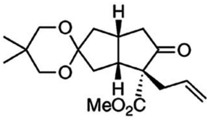
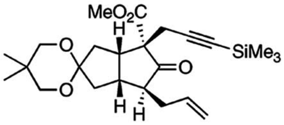
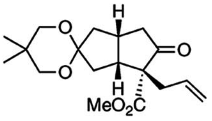
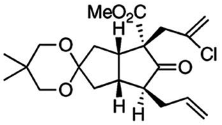
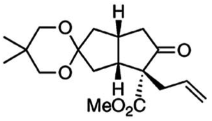
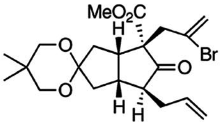
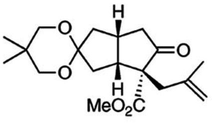
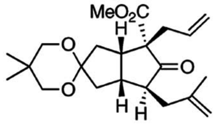
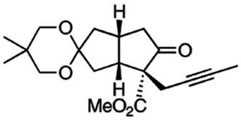
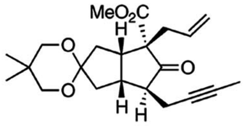
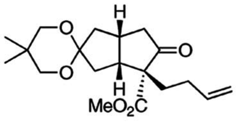
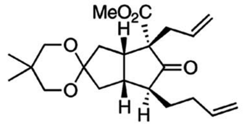
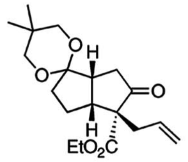
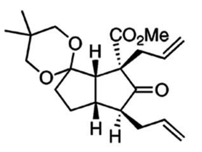
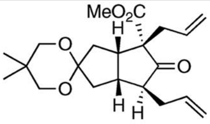
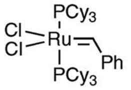
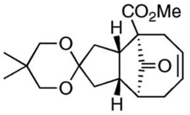
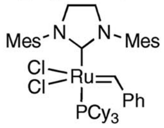
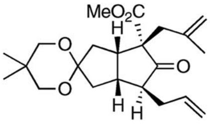
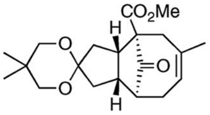
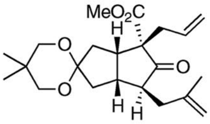
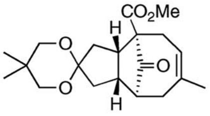
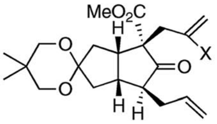
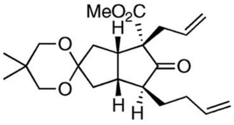
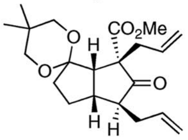
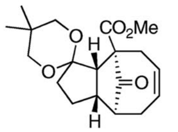
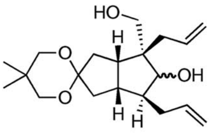
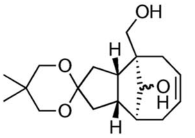
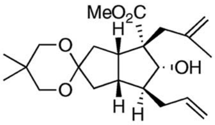
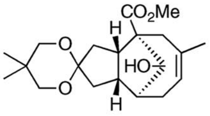
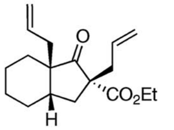
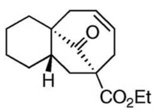
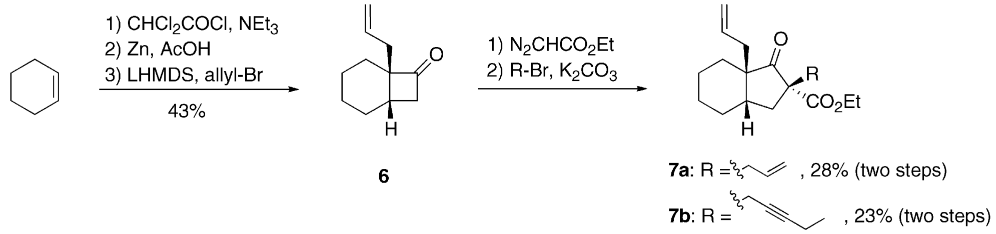
Entry	Substrate	Product	Yield (%)
1	 **2a**	 **3a**	86
2	 **2a**	 **3b**	81
3	 **2a**	 **3c**	30
4	 **2a**	 **3d**	91
5	 **2a**	 **3e**	71
6	 **2a**	 **3f**	48
7	 **2a**	 **3g**	75
8	 **2b**	 **3h**	81
9	 **2c**	 **3i**	86
10	 **2d**	 **3j**	72
11	 **2e**	 **3k**	70

Table 2. RCM of 1,8-dienes.

Entry	Substrate	Conditions	Product	Yield (%)
1	 **3a**	 **8a** (20 mol-%), CH_2Cl_2, reflux, 24 h	 **9a**	0
2	**3a**	**8a** (20 mol-%), toluene, reflux, 24 h	**9a**	20
3	**3a**	**8a** (10 mol-%), $\mathrm{Ti(O}i\mathrm{Pr)_4}$ (20 mol-%), CH_2Cl_2, reflux, 48 h	**9a**	50
4	**3a**	 **8b** (2 mol-%), CH_2Cl_2, reflux, 3 h	**9a**	84
5	 **3b**	**8b** (2 mol-%), CH_2Cl_2, reflux, 16 h	 **9b**	68
6	 **3h**	**8b** (2 mol-%), CH_2Cl_2, reflux, 16 h	 **9c**	70
7	 **3f**: X = Cl, **3g**: X = Br	**8b** (10 mol-%), CH_2Cl_2 or $Cl(CH_2)_2Cl$, reflux, 12 h	–	0
8	 **3j**	**8b** (10 mol-%), CH_2Cl_2 or $Cl(CH_2)_2Cl$, reflux, 12 h	–	0
9	 **3k**	**8b** (2 mol-%), CH_2Cl_2, reflux, 3 h	 **9d**	54
10	 **5a**	**8b** (1 mol-%), CH_2Cl_2, reflux, 3 h	 **9e**	92
11	 **5b**	**8b** (1 mol-%), CH_2Cl_2, reflux, 3 h	 **9f**	98
12	 **7a**	**8b** (2 mol-%), CH_2Cl_2, reflux, 3 h	 **9g**	75



Scheme 3.

with allyl bromide to give **6**, followed by ring expansion with ethyl diazoacetate[23] and a final alkylation step to give the bicyclo[4.3.0]nonanones **7a** and **7b** (Scheme 3).

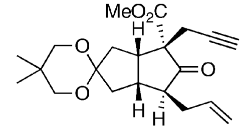
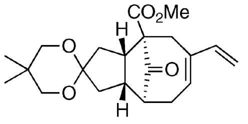
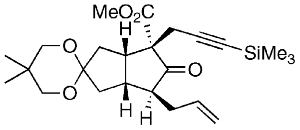
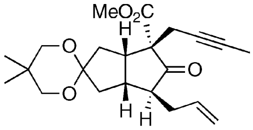
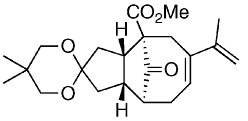
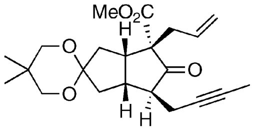
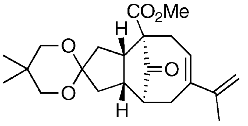
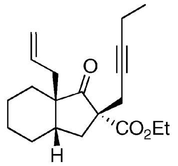
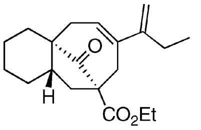
Metal-Catalyzed Cyclizations

Having in hand the 1,8-dienes or 1,8-enynes **3**, **5**, and **7**, we attempted the key cyclization step. A number of transition-metal-based catalysts are known to promote the cyclization of 1,*n*-dienes or 1,*n*-enynes by efficient C–C bond coupling. Many of these catalytic systems were screened without success. For example, under the ruthenium(II)-catalyzed cycloisomerization of 1,6-dienes described by Itoh,[24] the model 1,8-diene **3a** can only be epimerized to the internal 1,7- or 1,6-alkene if the reaction is carried out at high temperature, without observable cyclization. Similarly, 1,6-enynes with a true alkyne group are readily converted to bicyclo[3.1.0] derivatives by treatment with diazoalkanes in the presence of [Cp*RuCl(cod)],[25] but no cyclization resulted from the treatment of the 1,8-enyne **3c** under the same conditions (a partial decomposition was observed). Following the unique precedent from Overman and co-workers on the construction of a bridged bicyclic compound by a Heck coupling,[26] we submitted the vinyl bromide **3g** to various Heck reaction conditions but without any observable reaction. Our attempts to perform the cycloisomerization of the 1,8-enyne **3c** with $PtCl_2$,[27a–27d] $GaCl_3$,[28] $Ir(cod)_2Cl$,[29] and $AuClPPh_3/AgSbF_6$[27a–27g] essentially left the starting material unchanged, and some trials of an intramolecular Pauson–Khand reaction[27c,27d] with 1,8-enynes **3c**, **3i**, and **7b** led mostly to degradation products.

In sharp contrast to previous results, the catalytic ring-closing metathesis (RCM) of the 1,8-dienes and 1,8-enynes was rewarding, allowing the efficient regio- and stereocontrolled synthesis of many target bicyclo[4.2.1]nonanes.[30] In early attempts with precatalyst **8a** (20 mol-%), **3a** was recovered unchanged after 24 h in refluxing dichloromethane (Table 2, Entry 1), and we did observe some cyclization of **3a** in refluxing toluene to provide 20% of the expected bicyclo[4.2.1]nonane **9a** together with a considerable amount of degradation products (Table 2, Entry 2). Most probably and as previously observed,[31] the presence of the oxygen atom of the ketone in a 1,6-position relative to the vinylic methylene group is favorable for the formation of a stable and unproductive six-membered-ring, ruthenium-chelate complex. Indeed, the addition of 20 mol-% of $Ti(OiPr)_4$ to quench the Lewis basicity of the carbonyl groups and to avoid the formation of the chelate complex,[32] allowed the isolation of 50% of the RCM product **9a** after 48 h in refluxing dichloromethane in the presence of 10 mol-% of precatalyst **8a** (Table 2, Entry 3). Following these results, the activity of the next-generation Grubbs precatalyst **8b** was evaluated as excellent for our purpose, allowing the isolation of **9a** in 84% yield after 3 h in refluxing dichloromethane in the presence of 2 mol-% of **8b** without the addition of $Ti(OiPr)_4$ (Table 2, Entry 4). Under these optimized conditions, the unsymmetrical 1,8-diene **3b** underwent smooth RCM to provide the bicyclo[4.2.1]nonane **9b** together with 17% of the homocoupling product at the less substituted double bond (Table 2, Entry 5). The regioisomeric unsaturated precursor **3h** was also cyclized under the same conditions to give the corresponding regioisomeric bicyclo[4.2.1]nonane **9c** (Table 2, Entry 6). Following the work of Weinreb and Chao on the RCM of chloro-substituted olefins,[33] we submitted the chloro- and bromodienes **3f** and **3g** to RCM, and both substrates were inert under the conditions studied (Table 2, Entry 7). Also, and as earlier mentioned by Grubbs and co-workers,[34] the 1,9-diene **3j** does not undergo the RCM reaction to provide the corresponding bicyclo[5.2.1]decane (Table 2, Entry 8). The diallyl substrate **3k** underwent the RCM reaction with a little less efficiency than its regioisomer **3a** to give the expected cyclized alkene **9d** (Table 2, Entry 9). The two hydroxymethine-bridged substrates **5a**,**b** underwent extremely efficient RCM with only 1 mol-% of precatalyst **8b** to provide the cyclized alcohols **9e**,**f** (Table 2, Entries 10 and 11). In these cases, the RCM might be accelerated by the free hydroxy group as observed in related cases,[30,35] and/or the tetrahedral geometry of the bridge atom, which may allow better proximity of the two reactive methylene groups. Finally, the bicyclo[4.3.0]nonanone **7a** furnished 75% of the RCM product **9g** under the optimized conditions (Table 2, Entry 12).

The RCM of the 1,8-enynes **3c**–**e**,**i** and **7b** to furnish the corresponding dienes has also proven possible, and the results are reported in Table 3. Terminal alkynes are known to be bad partners in metathesis reactions with olefins. Indeed, the unsubstituted 1,8-enyne **3c** could not be cyclized by treatment with precatalyst **8b** under argon (Table 3, Entry 1), and even under ethylene,[36] the reaction was poorly efficient providing only 12% of the RCM product **10a** (Table 3, Entry 2). As an alternative for the preparation of **10a**, we tested the RCM reaction with trimethylsilyl-pro-

Table 3. RCM of 1,8-enynes.

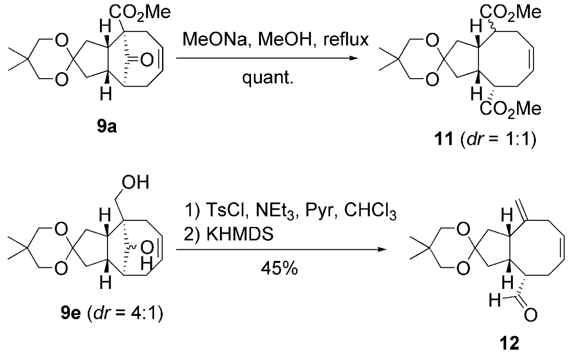
Entry	Substrate	Conditions	Product	Yield (%)
1	 **3c**	**8b** (20 mol-%), CH_2Cl_2, reflux, 24 h	 **10a**	0
2	**3c**	**8b** (5 × 2 mol-%), ethylene, CH_2Cl_2, reflux, 20 h	**10a**	12
3	 **3e**	**8b** (4 × 2 mol-%), $Cl(CH_2)_2Cl$, 120 °C, 24 h (sealed tube)	**10a**	21
4	 **3d**	**8b** (6 mol-%), CH_2Cl_2, reflux, 36 h	 **10b**	80
5	 **3i**	**8b** (6 mol-%), CH_2Cl_2, reflux, 36 h	 **10c**	76
6	 **7b**	**8b** (6 mol-%), CH_2Cl_2, reflux, 16 h	 **10d**	95

tected alkyne **3e**, which was expected to undergo in situ desilylation.[37] The desired desilylated diene **10a** was indeed obtained, but without much improvement in yield (Table 3, Entry 3). Alternatively, high yields of RCM products could be obtained with alkyl-substituted alkynes. As a matter of fact, the two regioisomeric 1,8-enynes **3d** and **3i** underwent efficient RCM to give the corresponding 1,3-dienes **10c** and **10d**, respectively (Table 3, Entries 4 and 5), and the RCM on substrate **7b** was nearly quantitative (Table 3, Entry 6).

Overall, the synthetic access to densely functionalized bicyclo[4.2.1]nonanes proposed here has been rendered possible by the high regio- and stereoselective introduction of two unsaturated alkyl chains on an α-activated cyclopentanone derivative followed by an efficient RCM cyclization. The high levels of stereocontrol of the alkylation steps derives from the conformational control allowed by the fused bicyclo[*x*.3.0] system, and the 1,3-*cis* configuration ensures good proximity of the two π-systems for the RCM to proceed. A major feature of this strategy is the unique regiocontrol offered by the dialkylation reaction, which translates into a totally selective access to the target bicyclo[4.2.1]nonanes (compare **9a** with **9d**, **9b** with **9c**, and **10b** with **10c**).

Postcyclization Reactions

To demonstrate the synthetic value of the bicyclo[4.2.1]nonanes **9**, we briefly tested some model fragmentation reactions with substrates **9a** and **9e**. In connection with our experience in the fragmentation of bridged bicyclic compounds,[3,9] we first looked at the direct retro-Dieckmann cleavage of the β-oxo ester **9a** and found that the desired functionalized cyclooctanoids **11** could be obtained quanti-



Scheme 4.

tatively by treatment with sodium methoxide in refluxing methanol, albeit as a 1:1 mixture of diastereomers (Scheme 4). Alternatively, a Grob-type fragmentation was attempted with the bridged bicyclo[4.2.1]nonanol **9e** (*dr* = 4:1). The corresponding primary monotosylate diastereomeric mixture (*dr* = 4:1)[15] was indeed stereoselectively transformed into the expected eight-membered ring **12** as a single diastereomer (*dr* > 25:1) by treatment with base (Scheme 4). This couple of postcyclization reactions illustrate well the synthetic possibilities that arise from the bicyclo[4.2.1]nonanes **9** and the various substitution patterns that might be obtained.

Conclusions

An efficient, domino, anionic, ring-cleavage/ring-reconstitution/alkylation sequence including a 1,3-shift of the ester group has been developed for the preparation of a variety of substrates of type **3**. With few exceptions, these substrates undergo highly efficient RCM reactions with precatalyst **8b** to provide the corresponding functionalized unsaturated bicyclo[4.2.1]nonanes **9** and **10**, thus establishing reliable access to these valuable bicyclic products. The attractiveness of the present approach resides in part in the total chemo- and regiocontrol and excellent stereocontrol that is achieved. The relevance of the temporary-bridge approach to cyclooctanoids from the properly functionalized bicyclo[4.2.1]nonane precursors has been demonstrated through the fragmentation of representative substrates. The functional-group tolerance of the domino-dialkylation/RCM sequence presented herein allows for the preparation of a variety of bridged bicyclic compounds, which can translate into a number of structurally distinct cyclooctanoids depending on the chosen fragmentation mode of the carbon bridge.

Experimental Section

General: All reactions were performed under argon in oven-dried round-bottomed glassware equipped with a magnetic Teflon-coated stirring bar. All reagents were obtained from commercial sources and used as supplied unless otherwise stated. MeOH was dried by refluxing with magnesium and then distilling under argon. Acetone was dried by refluxing with molecular sieves (4 Å) and then distilling under argon. K_2CO_3 was dried by prolonged storage at 140 °C in an oven. Pyridine and triethylamine were dried with solid KOH and distilled under argon. HMPA and toluene were dried by refluxing with CaH_2 and distilling under argon. THF was dried with sodium benzophenone ketyl. Petrol ether refers to the fraction of petroleum ether that was distilled between 40 and 65 °C. Dimethyl carbonate was distilled prior to use. The reactions were monitored by TLC, which were performed with Merck $60F_{254}$ plates and visualized with an ethanolic solution of *p*-anisaldehyde and sulfuric acid or an ethanolic solution of phosphomolybdic acid. Flash chromatography was performed with Merck 230–400 mesh silica gel. NMR spectroscopic data were recorded with a Bruker AC 200, Avance 300, or Avance 400 spectrometer in $CDCl_3$, and chemical shifts (δ) are given in ppm relative to the residual non-deuterated signal for ^1H NMR ($CHCl_3$: δ = 7.25 ppm) and relative to the deuterated solvent signal for ^{13}C NMR ($CDCl_3$: δ = 77.0 ppm); $^3J_{H,H}$ coupling constants (*J*) are in Hz, and the classical abbreviations are used to describe the signal multiplicity; peak assignment and relative configurations have been established from standard COSY, NOESY, HMQC, and HMBC experiments. Mass spectra were recorded with an API III Plus Sciex spectrometer equipped with an electrospray ionization source and a triple quadrupole or with a Bruker Esquire 6000 spectrometer equipped with an electrospray ionization source and an ion trap detector. Melting points are uncorrected and were measured with a Büchi B-540 apparatus. Elemental analysis were performed with a Thermo Finnigan EA 1112 analyzer.

General Procedure for Compounds of Type 2 and 7: The procedure for **2a** is representative for compounds of type **2** and **7** (except **2d**).

Compound 2a: The bicyclic monoprotected β-oxo ester obtained after carbonylation of **1**[13] (4.52 g, 16.0 mmol) was dissolved in acetone (100 mL). K_2CO_3 (8.78 g, 63.5 mmol) and allyl bromide (2.75 mL, 31.8 mmol) were added to this solution. The mixture was refluxed for 3 h, cooled to room temp., filtered through a short pad of Celite, and concentrated. The crude product was purified by flash chromatography on silica gel, eluting with Et_2O and petrol ether to give 3.68 g (71%) of **2a**. Recrystallization from chloroform afforded colorless crystals suitable for X-ray analysis. R_f = 0.42 (Et_2O/petrol ether, 70:30); m.p. 61 °C. IR (film): $\tilde{\nu}$ = 2951, 2858, 1748, 1732, 1435, 1328, 1226, 1119, 1017, 924, 773 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 5.66 (ddt, *J* = 17.0, 9.6, 7.6 Hz, 1 H), 5.03–5.12 (m, 2 H), 3.68 (s, 3 H), 3.46 (s, 2 H), 3.41 (s, 2 H), 2.79 (dt, *J* = 11.3, 7.9 Hz, 1 H), 2.50–2.70 (m, 4 H), 2.39 (ddd, *J* = 14.0, 7.9, 1.7 Hz, 1 H), 2.33 (d, *J* = 9.4 Hz, 1 H), 2.28 (ddd, *J* = 13.6, 7.9, 1.5 Hz, 1 H), 1.76 (dd, *J* = 13.6, 4.5 Hz, 1 H), 1.68 (dd, *J* = 13.6, 11.3 Hz, 1 H), 0.94, (s, 3 H), 0.92 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 214.3 (C), 171.3 (C), 132.4 (CH), 119.8 (CH_2), 109.2 (C), 73.2 (CH_2), 71.3 (CH_2), 63.2 (C), 52.2 (CH_3), 47.1 (CH), 44.9 (CH_2), 41.2 (CH_2), 39.3 (CH_2), 36.8 (CH_2), 33.8 (CH), 30.1 (C), 22.1 (CH_3), 22.1 (CH_3) ppm. MS (ESI$^+$): *m*/*z* = 323 [M + H]$^+$, 345 [M + Na]$^+$, 361 [M + K]$^+$. $C_{18}H_{26}O_5$ (322.40): calcd. C 67.06, H 8.13; found C 66.75, H 8.04.

Compound 2b: Colorless oil; yield: 616 mg (81%); R_f = 0.31 (Et_2O/petrol ether, 30:70). IR (film): $\tilde{\nu}$ = 2950, 2863, 1732, 1643, 1438, 1324, 1119, 1012, 906, 773, 733 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 4.79 (t, *J* = 1.5 Hz, 1 H), 4.67 (br. s, 1 H), 3.66 (s, 3 H), 3.42, (s, 2 H), 3.37 (s, 2 H), 2.75 (dt, *J* = 11.1, 8.5 Hz, 1 H), 2.67 (d, *J* = 14.1 Hz, 1 H), 2.55 (d, *J* = 14.1 Hz, 1 H), 2.43–2.69 (m, 2 H), 2.15–2.40 (m, 3 H), 1.75 (dd, *J* = 13.8, 3.6 Hz, 1 H), 1.57 (s, 3 H), 1.56 (dd, *J* = 11.1, 2.4 Hz, 1 H), 0.90 (s, 3 H), 0.89 (s, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 213.7 (C), 171.4 (C), 140.7 (C), 116.0 (CH_2), 108.9 (C), 72.7 (CH_2), 71.5 (CH_2), 63.5 (C), 52.1 (CH_3), 47.0 (CH), 44.4 (CH_2), 42.8 (CH_2), 41.0 (CH_2), 37.0 (CH_2), 33.6 (CH), 30.1 (C), 23.4 (CH_3), 22.4 (CH_3), 22.3 (CH_3) ppm. MS (ESI$^+$): *m*/*z* = 337 [M + H]$^+$, 354 [M + NH_4]$^+$, 359 [M + Na]$^+$, 375 [M + K]$^+$, 386 [M + NH_4 + CH_3OH]$^+$.

Compound 2c: Colorless oil; yield: 584 mg (90%); R_f = 0.31 (Et_2O/petrol ether, 30:70). IR (film): $\tilde{\nu}$ = 2951, 2862, 1737, 1436, 1325, 1237, 1119, 1014, 914, 733 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 3.67 (s, 3 H), 3.49 (s, 2 H), 3.42 (s, 2 H), 3.02 (dt, *J* = 10.3, 8.6 Hz, 1 H), 2.79 (ddd, *J* = 10.3, 8.7, 2.5 Hz, 1 H), 2.67 (q, *J* = 2.6 Hz, 2 H), 2.58 (d, *J* = 8.6 Hz, 1 H), 2.27–2.53 (m, 3 H), 1.70 (t, *J* = 2.6 Hz, 3 H), 1.64–1.83 (m, 2 H), 0.96 (s, 3 H), 0.92 (s, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 214.6 (C), 171.0 (C), 108.8 (C), 78.1 (C), 74.0 (C), 72.9 (CH_2), 71.3 (CH_2), 62.5 (C), 52.2 (CH_3), 46.9 (CH), 45.2 (CH_2), 41.0 (CH_2), 36.4 (CH_2), 34.2 (CH), 30.1 (C), 25.0 (CH_2), 22.4 (CH_3), 22.3 (CH_3), 3.5 (CH_3) ppm. MS

(ESI$^+$): *m*/*z* = 335 [M + H]$^+$, 352 [M + NH_4]$^+$, 357 [M + Na]$^+$, 373 [M + K]$^+$, 384 [M + NH_4 + CH_3OH]$^+$.

Compound **2e** was obtained from the regioisomeric, bicyclic, monoprotected, β-oxo ester[38] according to the procedure described for **2a**. Colorless oil; yield: 148 mg (67%); R_f = 0.62 (Et_2O/petrol ether, 70:30). IR (film): $\tilde{\nu}$ = 3078, 2955, 2867, 1729, 1640, 1469, 1362, 1217, 1099, 1029, 919 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.70 (m, 1 H), 5.04–5.15, (m, 2 H), 4.08–4.21 (m, 2 H), 3.52 (d, *J* = 11.2 Hz, 1 H), 3.41–3.48 (m, 2 H), 3.34 (d, *J* = 11.2 Hz, 1 H), 2.75–2.85 (m, 2 H), 2.35–2.65 (m, 4 H), 1.74–2.08 (m, 3 H), 1.45–1.60 (m, 1 H), 1.23 (t, *J* = 7.2 Hz, 3 H), 0.98 (s, 3 H), 0.91 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 213.8 (C), 170.6 (C), 132.5 (CH), 119.5 (CH_2), 108.7 (C), 72.6 (CH_2), 71.7 (CH_2), 63.6 (C), 61.0 (CH_2), 47.2 (CH), 39.9 (CH_2), 39.0 (CH_2), 32.5 (CH_2), 25.4 (CH_2), 43.6 (CH), 30.0 (C), 22.5 (CH_3), 22.5 (CH_3), 14.1 (CH_3) ppm. MS (ESI$^+$): *m*/*z* = 337 [M + H]$^+$, 354 [M + NH_4]$^+$, 359 [M + Na]$^+$, 375 [M + K]$^+$, 386 [M + NH_4 + CH_3OH]$^+$.

Compound 2d: 4-bromobutene (192 mg, 1.42 mmol) and potassium iodide (236 mg, 1.42 mmol) were dissolved in acetone (15 mL), and the mixture was refluxed for 2 h. K_2CO_3 (392 mg, 2.84 mmol) and β-oxo ester **1** (200 mg, 0.71 mmol) were added to the solution, which was refluxed for additional 3 h. The reaction mixture was cooled to room temp., diluted with Et_2O, filtered through a short pad of Celite, and concentrated. The crude product was purified by flash chromatography on silica gel, eluting with Et_2O and petrol ether to give 127 mg (53%) of **2d** as a colorless oil. R_f = 0.53 (Et_2O/petrol ether, 70:30). IR (film): $\tilde{\nu}$ = 2912, 2863, 1734, 1641, 1442, 1327, 1210, 1119, 1013, 912, 758 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.68 (m, 1 H), 4.87–4.98 (m, 2 H), 3.67 (s, 3 H), 3.44 (s, 2 H), 3.38 (s, 2 H), 2.53–2.78 (m, 3 H), 2.19–2.48 (m, 3 H), 2.02–2.17 (m, 1 H), 1.84–1.98 (m, 2 H), 1.69–1.82 (m, 2 H), 1.64 (dd, *J* = 13.5, 11.0 Hz, 1 H), 0.92 (s, 3 H), 0.90 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 214.1 (C), 171.4 (C), 137.4 (CH), 115.2 (CH_2), 108.9 (C), 72.8 (CH_2), 71.5 (CH_2), 64.1 (C), 52.0 (CH_3), 48.5 (CH), 44.7 (CH_2), 41.0 (CH_2), 36.9 (CH_2), 34.5 (CH_2), 33.8 (CH), 30.1 (C), 28.7 (CH_2), 22.4 (CH_3), 22.4 (CH_3) ppm. MS (ESI$^+$): *m*/*z* = 337 [M + H]$^+$, 354 [M + NH_4]$^+$, 359 [M + Na]$^+$, 375 [M + K]$^+$, 391 [M + Na + CH_3OH]$^+$.

General Procedure for Compounds of Type 3: The procedure for **3e** is representative for compounds of type **3**.

Compound 3e: To a solution of **2a** (161 mg, 0.50 mmol) in anhydrous methanol (5 mL) was added sodium methoxide (27 mg, 0.50 mmol), and the reaction mixture was stirred under argon at reflux for 1 h. Toluene was then added (10 mL), and the methanol was evaporated by azeotropic distillation. When the methanol was totally removed, 3-(trimethylsilyl)propargyl bromide (172 mg, 0.90 mmol) was added, and the reaction mixture was heated at reflux for 16 h and cooled to room temp. Saturated aqueous NH_4Cl was added, and the aqueous layer was extracted three times with Et_2O. The combined organic layers were washed with brine, dried with anhydrous sodium sulfate, and concentrated. The crude product was purified by flash chromatography on silica gel, eluting with Et_2O in petrol ether to give 154 mg (71%) of **3e** as a colorless oil. R_f = 0.55 (AcOEt/petrol ether, 30:70). IR (film): $\tilde{\nu}$ = 2948, 2863, 1750, 1726, 1433, 1248, 1111, 1016, 846 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.76 (m, 1 H), 4.99–5.10 (m, 2 H), 3.43 (s, 3 H), 3.50 (s, 2 H), 3.43 (s, 2 H), 2.98 (dt, *J* = 12.5, 7.6 Hz, 1 H), 2.80 (d, *J* = 1.7 Hz, 2 H), 2.53–2.64 (m, 1 H), 2.43–2.52 (m, 3 H), 2.34 (dd, *J* = 13.7, 7.5 Hz, 1 H), 2.13 (dt, *J* = 13.8, 7.7 Hz, 1 H), 1.71–1.79 (m, 1 H), 1.63 (t, *J* = 12.5 Hz, 1 H), 0.97 (s, 3 H), 0.94 (s, 3 H), 0.10 (s, 9 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 214.0 (C), 171.0 (C), 135.7 (CH), 116.9 (CH_2), 108.8 (C), 102.4 (C), 87.1 (C), 73.0 (CH_2), 71.3 (CH_2), 61.6 (C), 55.4 (CH), 52.4 (CH_3), 45.0 (CH), 41.0 (CH_2), 40.6 (CH), 36.4 (CH_2), 33.1 (CH_2), 30.2 (C), 25.8 (CH_2), 22.5 (CH_3), 22.4 (CH_3), 0.0 (CH_3) ppm. MS (ESI$^+$): *m*/*z* = 433 [M + H]$^+$, 450 [M + NH_4]$^+$, 455 [M + Na]$^+$, 471 [M + K]$^+$.

Compounds **3a**, **3b**, **3d**, **3h**, and **3i** were previously fully characterized.[11]

Compound 3c: White crystals; yield: 74 mg (30%); R_f = 0.38 (AcOEt/petrol ether, 20:80); m.p. 54–63 °C. IR (film): $\tilde{\nu}$ = 3279, 3074, 2952, 2862, 2248, 1737, 1640, 1436, 1325, 1238, 1112, 1016, 915 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 5.75 (ddt, *J* = 16.6, 13.8, 6.8 Hz, 1 H), 5.04 (m, 2 H), 3.67 (s, 3 H), 3.48 (s, 2 H), 3.42 (s, 2 H), 2.99 (dt, *J* = 11.9, 7.7 Hz, 1 H), 2.81 (d, *J* = 2.6 Hz, 2 H), 2.44–2.64 (m, 4 H), 2.38 (dd, *J* = 11.9, 7.7 Hz, 1 H), 2.21 (dd, *J* = 15.8, 7.4 Hz, 1 H), 1.89 (t, *J* = 2.6 Hz, 1 H) 1.68 (t, *J* = 11.9 Hz, 1 H), 1.25 (dt, *J* = 15.8, 7.2 Hz, 1 H), 0.95, (s, 3 H), 0.93 (s, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 213.8 (C), 170.8 (C), 135.4 (CH), 117.0 (CH_2), 108.5 (C), 80.0 (CH), 72.8 (CH_2), 70.9 (CH_2), 70.5 (C), 61.3 (C), 55.1 (CH), 52.3 (CH_3), 44.9 (CH), 40.4 (CH_2), 40.1 (CH), 36.5 (CH_2), 32.7 (CH_2), 30.0 (C), 23.8 (CH_2), 22.3 (CH_3), 22.3 (CH_3) ppm. MS (ESI$^+$): *m*/*z* = 361 [M + H]$^+$, 378 [M + NH_4]$^+$, 383 [M + Na]$^+$, 399 [M + K]$^+$.

Compound 3f: Colorless oil; yield: 43 mg (48%); R_f = 0.45 (Et_2O/petrol ether, 50:50). IR (film): $\tilde{\nu}$ = 2954, 2865, 1748, 1732, 1631, 1434, 1239, 1116, 1020, 909 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.77 (m, 1 H), 5.30 (s, 1 H), 5.23 (s, 1 H), 5.01–5.11 (m, 2 H), 3.70 (s, 3 H), 3.49 (s, 2 H), 3.43 (s, 2 H), 2.96 (dt, *J* = 12.5, 7.9 Hz, 1 H), 3.03 (d, *J* = 6.8 Hz, 2 H), 2.59–2.70 (m, 1 H), 2.26–2.52 (m, 4 H), 2.09 (dt, *J* = 14.1, 7.5 Hz, 1 H), 1.79 (dd, *J* = 14.1, 4.1 Hz, 1 H), 1.65 (t, *J* = 12.5 Hz, 1 H), 0.96 (s, 3 H), 0.95 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 213.7 (C), 171.2 (C), 137.2 (C), 135.8 (CH), 118.3 (CH_2), 117.0 (CH_2), 108.9 (C), 73.0 (CH_2), 71.4 (CH_2), 62.1 (C), 55.4 (CH), 52.5 (CH_3), 43.7 (CH), 43.3 (CH_2), 40.7 (CH_2), 40.7 (CH), 37.2 (CH_2), 34.2 (CH_2), 30.2 (C), 22.5 (CH_3), 22.5 (CH_3) ppm. MS (ESI$^+$): *m*/*z* = 397/399 [M + H]$^+$, 414/416 [M + NH_4]$^+$, 419/421 [M + Na]$^+$, 435/437 [M + K]$^+$.

Compound 3g: Slightly yellow oil; yield: 89 mg (75%); R_f = 0.43 (AcOEt/petrol ether, 20:80). IR (film): $\tilde{\nu}$ = 2953, 2861, 1734, 1623, 1435, 1325, 1223, 1114, 1012, 909 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.78 (ddt, *J* = 16.8, 10.0, 7.7 Hz, 1 H), 5.66 (d, *J* = 1.4 Hz, 1 H), 5.56 (d, *J* = 1.4 Hz, 1 H), 5.01–5.13 (m, 2 H), 3.70 (s, 3 H), 3.49 (s, 2 H), 3.43 (s, 2 H), 3.14 (s, 2 H), 2.98 (dt, *J* = 12.5, 5.2 Hz, 1 H), 2.59–2.71 (m, 1 H), 2.25–2.55 (m, 5 H), 1.78 (dd, *J* = 10.0, 2.0 Hz, 1 H), 1.65 (t, *J* = 12.5 Hz, 1 H), 0.96 (s, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 213.5 (C), 171.0 (C), 135.7 (CH), 127.4 (C), 117.1 (CH_2), 112.9 (CH_2), 108.9 (C), 73.0 (CH_2), 71.4 (CH_2), 62.6 (C), 55.3 (CH), 52.5 (CH_3), 45.0 (CH_2), 43.6 (CH), 40.7 (CH_2), 40.7 (CH), 37.2 (CH_2), 34.1 (CH_2), 30.2 (C), 22.5 (CH_3), 22.5 (CH_3) ppm. MS (ESI$^+$): *m*/*z* = 441/443 [M + H]$^+$, 458/460 [M + NH_4]$^+$, 463/465 [M + Na]$^+$, 479/481 [M + K]$^+$.

Compound 3j: Colorless oil; yield: 108 mg (72%); R_f = 0.50 (AcOEt/petrol ether, 30:70). IR (film): $\tilde{\nu}$ = 2955, 2849, 1731, 1637, 1437, 1325, 1255, 1114, 1008, 908, 796 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.79 (ddt, *J* = 17.0, 10.2, 6.6 Hz, 1 H), 5.64 (ddt, *J* = 17.5, 10.3, 7.4 Hz, 1 H), 4.96–5.12 (m, 4 H), 3.69 (s, 3 H), 3.49 (s, 2 H), 3.43 (s, 2 H), 2.74 (dt, *J* = 12.3, 7.9 Hz, 1 H), 2.57 (t, *J* = 7.0 Hz, 2 H), 2.47 (ddd, *J* = 14.0, 8.3, 1.7 Hz, 1 H), 2.18–2.48 (m, 4 H), 2.08–2.18 (m, 2 H), 1.81 (dd, *J* = 14.0, 4.2 Hz, 1 H), 1.32–1.46 (m, 2 H), 0.95 (s, 3 H), 0.97 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 215.3 (C), 171.7 (C), 138.1 (CH), 132.7 (CH), 119.8 (CH_2), 115.4 (CH_2), 109.1 (C), 73.0 (CH_2), 71.5 (CH_2), 62.8 (C), 54.8 (CH), 52.2 (CH_3), 45.1 (CH), 40.9 (CH_2), 40.7 (CH), 39.6 (CH_2), 36.9 (CH_2), 31.3 (CH_2), 28.8 (CH_2), 30.2 (C), 22.5 (CH_3), 22.4 (CH_3) ppm. MS (ESI$^+$): m/z = 377 [M + H]$^+$, 394 [M + NH_4]$^+$, 399 [M + Na]$^+$, 415 [M + K]$^+$.

Compound 3k: Colorless oil; yield: 38 mg (70%); R_f = 0.57 (AcOEt/petrol ether, 20:80). IR (film): ṽ = 2952, 2857, 1739, 1640, 1459, 1324, 1216, 1049, 1011, 917 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.56–5.84 (m, 2 H), 4.99–5.19 (m, 4 H), 3.65 (s, 3 H), 3.53 (d, J = 11.6 Hz, 1 H), 3.43 (t, J = 11.6 Hz, 2 H), 3.30 (dd, J = 11.6, 1.4 Hz, 1 H), 2.84 (d, J = 9.4 Hz, 1 H), 2.59–2.65 (m, 2 H), 2.43–2.58 (m, 2 H), 2.29–2.43 (m, 1 H), 2.09–2.24 (m, 2 H), 1.92–2.08 (m, 2 H), 1.64 (m, 1 H), 0.81 (s, 3 H), 1.06 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 214.2 (C), 170.8 (C), 135.7 (CH), 133.3 (CH), 119.7 (CH_2), 117.2 (CH_2), 109.0 (C), 72.8 (CH_2), 72.0 (CH_2), 62.6 (C), 55.5 (CH), 54.2 (CH), 52.0 (CH_3), 40.4 (CH_2), 40.5 (CH), 33.9 (CH_2), 31.2 (CH_2), 30.0 (C), 28.0 (CH_2), 23.3 (CH_3), 22.6 (CH_3) ppm. MS (ESI$^+$): m/z = 363 [M + H]$^+$, 380 [M + NH_4]$^+$, 385 [M + Na]$^+$, 401 [M + K]$^+$, 412 [M + NH_4 + CH_3OH]$^+$.

Compounds **5a** and **5b** were previously fully characterized.[11]

Compound 6: To LHMDS (1.0 M solution, 4.8 mL, 4.8 mmol) in hexane was added dropwise at –78 °C a solution of (±)-(1*S*,6*S*)-bicyclo[4.2.0]octan-7-one[21] (501 mg, 4.03 mmol) in THF (7 mL). The mixture was stirred at –78 °C for 30 min, whereupon allyl bromide (3.50 mL, 40.4 mmol) was added at the same temperature. The mixture was stirred at –78 °C for 1 h and then warmed slowly to room temp. over 10 h. Hydrochloric acid (1 N, 10 mL) was added, and the aqueous layer was extracted three times with Et_2O. The combined organic layers were washed with brine, dried with anhydrous Na_2SO_4, filtered, and concentrated. The crude product was purified by flash chromatography, eluting with Et_2O and petrol ether to give 351 mg (53%) of **6** as a colorless oil. R_f = 0.47 (Et_2O/petrol ether, 10:90). IR (film): ṽ = 2930, 2856, 1772, 1639, 1448, 1403, 1179, 1055, 998, 915 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.78 (ddt, J = 7.4, 10.9, 16.1 Hz, 1 H), 5.03–5.09 (m, 2 H), 2.98 (dd, J = 16.9, 9.1 Hz, 1 H), 2.85 (dd, J = 16.9, 7.2 Hz, 1 H), 2.27 (dd, J = 7.3, 1.1 Hz, 1 H), 2.10–2.34 (m, 1 H), 1.27–1.88 (m, 9 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 212.1 (C), 133.7 (CH), 117.6 (CH_2), 62.6 (C), 47.8 (CH_2), 40.1 (CH_2), 27.7 (CH), 26.9 (CH_2), 25.5 (CH_2), 20.8 (CH_2), 20.1 (CH_2) ppm. MS (ESI$^+$): m/z = 165 [M + H]$^+$, 182 [M + NH_4]$^+$, 187 [M + Na]$^+$.

Compounds 7a and 7b: A solution of $SbCl_5$ (1 M in dichloromethane, 0.7 mL, 0.7 mmol) was added to a solution of **6** (1.65 g, 10.0 mmol) in dichloromethane (35 mL) at –78 °C. The mixture was stirred at that temperature for 20 min, and ethyl diazoacetate (1.72 g, 15.1 mmol) was added dropwise over 90 min. The mixture was stirred at –78 °C for 4 h, warmed to 0 °C, and a saturated solution of $NaHCO_3$ was added carefully. The organic layer was separated, the aqueous layer was extracted once with dichloromethane, and the combined organic layers were washed with brine, dried with anhydrous Na_2SO_4, filtered, and concentrated. The crude product was purified by flash chromatography, eluting with Et_2O in petrol ether to give 1.50 g (60%) of the expected β-oxo ester as an inseparable mixture of two diastereomers (*dr* = 65:35). R_f = 0.45 (Et_2O/petrol ether, 10:90). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.55–5.92 (m, 1 H), 5.00–5.14 (m, 2 H), 4.15–4.30 (m, 2 H), 3.37 (t, J = 7.6 Hz, 0.5 H), 3.15 (t, J = 10.6 Hz, 0.5 H), 1.88–2.48 (m, 5 H), 1.60–1.86 (m, 2 H), 1.34–1.54 (m, 4 H), 1.23–1.34 (m, 5 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 214.1 (C), 213.3 (C), 170.0 (C), 169.8 (C), 134.1 (CH), 133.2 (CH), 118.4 (CH_2), 118.4 (CH_2), 61.6 (CH_2), 61.4 (CH_2), 55.0 (CH), 53.5 (C), 52.1 (CH), 51.8 (C), 38.5 (CH_2), 37.9 (CH), 36.9 (CH_2), 35.5 (CH), 28.7 (CH_2), 28.4 (CH_2), 27.5 (CH_2), 27.3 (CH_2), 24.1 (CH_2), 23.1 (CH_2), 22.8 (CH_2), 21.3 (CH_2), 20.5 (CH_2), 17.4 (CH_2), 14.8 (CH_3), 14.3 (CH_3) ppm. MS (ESI$^+$): m/z = 251 [M + H]$^+$, 268 [M + NH_4]$^+$, 273 [M + Na]$^+$, 518 [2 M + NH_4]$^+$, 523 [2 M + Na]$^+$, 539 [2 M + K]$^+$.

Compounds **7a** and **7b** were obtained from the above β-oxo ester according to the procedure described for **2a** with allyl bromide and 1-bromobut-2-yne, respectively.

Compound 7a: Colorless oil, yield: 228 mg (47%); R_f = 0.50 (Et_2O/petrol ether, 10:90). IR (film): ṽ = 3075, 2930, 2860, 1721, 1638, 1443, 1309, 1202, 1147, 1098, 1033, 1003, 916 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.56–5.81 (m, 2 H), 5.01–5.13 (m, 4 H), 4.20 (dq, J = 7.1, 4.5 Hz, 1 H), 4.17 (dq, J = 7.1, 4.5 Hz, 1 H), 2.56–2.66 (m, 2 H), 2.31–2.46 (m, 2 H), 2.14–2.25 (m, 1 H), 2.12 (dd, J = 14.0, 8.1 Hz, 1 H), 1.83 (dd, J = 13.1, 6.8 Hz, 1 H), 1.32–1.70 (m, 7 H), 1.27 (t, J = 7.1 Hz, 3 H), 1.14–1.24 (m, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 215.5 (C), 171.4 (C), 134.4 (CH), 133.5 (CH), 119.0 (CH_2), 118.3 (CH_2), 61.5 (CH_2), 59.8 (C), 52.2 (C), 37.2 (CH_2), 36.5 (CH_2), 33.0 (CH), 31.2 (CH_2), 28.2 (CH_2), 23.5 (CH_2), 21.3 (CH_2), 20.1 (CH_2), 14.2 (CH_3) ppm. MS (ESI$^+$): m/z = 291 [M + H]$^+$, 308 [M + NH_4]$^+$, 313 [M + Na]$^+$, 329 [M + K]$^+$.

Compound 7b: Colorless oil; yield: 147 mg (38%); R_f = 0.50 (Et_2O/petrol ether, 10:90). IR (film): ṽ = 2931, 1726, 1633, 1559, 1456, 1202, 1030, 918 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.54–5.71 (m, 1 H), 4.96–5.08 (m, 2 H), 4.20 (m, 2 H), 2.65–2.78 (m, 2 H), 2.20–2.45 (m, 4 H), 2.02–2.18 (m, 3 H), 1.32–1.72 (m, 8 H), 1.27 (t, J = 7.0 Hz, 3 H), 1.08 (t, J = 7.6 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 215.3 (C), 171.0 (C), 134.7 (CH), 118.4 (CH_2), 84.1 (C), 75.2 (C), 62.0 (CH_2), 60.0 (C), 52.7 (C), 36.7 (CH_2), 33.5 (CH), 31.9 (CH_2), 28.2 (CH_2), 23.9 (CH_2), 23.6 (CH_2), 21.5 (CH_2), 20.2 (CH_2), 14.2 (CH_3), 14.2 (CH_3), 12.5 (CH_2) ppm.

General Procedure for Compounds of Type 9: The procedure for **9g** is representative for compounds of type **9** and **10b**–**d**.

Compound 9g: To a solution of **7a** (35 mg, 0.12 mmol) in dichloromethane (20 mL) was added precatalyst **8b** (2 mg, 2 mol-%, see Tables 2 and 3 for other substrates), and the resulting solution was refluxed for 3 h and concentrated. The crude product was purified by flash chromatography, eluting with Et_2O and petrol ether to give 24 mg (75%) of **9g** as a brown oil. R_f = 0.63 (Et_2O/petrol ether, 70:30). IR (film): ṽ = 2930, 2857, 1744, 1722, 1447, 1366, 1274, 1232, 1187, 1025, 912, 733 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.54–5.66 (m, 1 H), 5.43–5.54 (m, 1 H), 4.22 (q, J = 7.2 Hz, 2 H), 2.58 (m, 1 H), 2.40 (ddt, J = 12.1, 5.9, 1.0 Hz, 1 H), 2.35 (dd, J = 13.9, 7.9 Hz, 1 H), 2.07–2.20 (m, 2 H), 1.90–2.04 (m, 3 H), 1.72–1.82 (m, 1 H), 1.52–1.68 (m, 2 H), 1.39 (dd, J = 13.6, 3.3 Hz, 1 H), 1.29 (t, J = 7.2 Hz, 3 H), 1.21 (dd, J = 13.6, 4.1 Hz, 1 H), 1.09 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 216.1 (C), 172.6 (C), 127.5 (CH), 123.8 (CH), 61.5 (CH_2), 58.1 (C), 54.0 (C), 42.4 (CH_2), 41.9 (CH), 36.1 (CH_2), 35.7 (CH_2), 32.2 (CH_2), 32.2 (CH_2), 24.5 (CH_2), 23.5 (CH_2), 14.2 (CH_3) ppm. MS (ESI$^+$): m/z = 263 [M + H]$^+$, 280 [M + NH_4]$^+$, 285 [M + Na]$^+$, 301 [M + K]$^+$.

Compound 9d: Brown oil; yield: 27 mg (54%); R_f = 0.35 (AcOEt/petrol ether, 20:80). IR (film): ṽ = 2952, 2868, 1737, 1470, 1431, 1354, 1241, 1124, 1023, 911 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.63 (m, 2 H), 3.67 (s, 3 H), 3.44 (s, 2 H), 3.31 (d, J = 11.4 Hz, 1 H), 3.23 (d, J = 11.4 Hz, 1 H), 2.92 (d, J = 8.6 Hz, 1 H), 2.76 (m, 1 H), 2.55 (t, J = 4.0 Hz, 1 H), 2.40 (td, J = 8.7, 5.6 Hz, 1 H), 2.22–2.32 (m, 3 H), 1.98–2.18 (m, 2 H), 1.84–1.96 (m, 1 H), 1.40–1.54 (m, 1 H), 0.89 (s, 3 H), 0.93 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 217.2 (C), 171.3 (C), 127.2 (CH), 124.9 (CH), 109.9 (C), 73.3 (CH_2), 71.5 (CH_2), 60.4 (C), 55.5 (CH), 54.7 (CH), 52.1 (CH_3), 42.9 (CH), 37.4 (CH_2), 32.8 (CH_2), 32.6 (CH_2), 29.4 (CH_2), 30.0 (C), 22.8 (CH_3), 22.6 (CH_3) ppm. MS (ESI$^+$): m/z = 335 [M

+ H]$^+$, 352 [M + NH_4]$^+$, 357 [M + Na]$^+$, 367 [M + H + CH_3OH]$^+$, 384 [M + NH_4 + CH_3OH]$^+$, 389 [M + Na + CH_3OH]$^+$.

Compound 10a. From 3c: Ethylene was bubbled through a stirred solution of **3c** (83 mg, 0.23 mmol) in dichloromethane (38 mL) for 5 min. Precatalyst **8b** (4 mg, 2 mol-%) was added, and the resulting solution was refluxed for 4 h. This operation was repeated 4 additional times (total: 10 mol-% of **8b** and 20 h of reaction time), and the reaction mixture was concentrated. The crude product was purified by flash chromatography, eluting with Et_2O in petrol ether to give 10 mg (12%) of **10a** as a brown oil. **From 3e:** A solution of **3e** (130 mg, 0.30 mmol) in dichloroethane (50 mL) was placed in a 250-mL Schlenk tube. Precatalyst **8b** (5 mg, 2 mol-%) was added, and the resulting solution was heated at 120 °C (oil bath temperature) for 6 h. This operation was repeated 3 additional times (total: 8 mol-% of **8b** and 24 h of reaction time), and the reaction mixture was concentrated. The crude product was purified by flash chromatography, eluting with Et_2O and petrol ether to give 45 mg of starting material **3e** and 23 mg (21%) of **10a** as a brown oil. R_f = 0.51 (Et_2O/petrol ether, 70:30). IR (film): $\tilde{\nu}$ = 2959, 2866, 1736, 1727, 1435, 1259, 1110, 1017 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.32 (dd, J = 17.2, 10.8 Hz, 1 H), 5.79 (m, 1 H), 5.17 (d, J = 17.2 Hz, 1 H), 4.96 (d, J = 10.8 Hz, 1 H), 3.76 (s, 3 H), 3.40 (s, 2 H), 3.42 (s, 2 H), 3.11 (d, J = 16.6 Hz, 1 H), 2.34–2.64 (m, 6 H), 2.17–2.28 (m, 2 H), 1.53–1.73 (m, 2 H), 0.92 (s, 3 H), 0.91 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 217.2 (C), 171.7 (C), 142.6 (CH), 135.2 (C), 129.7 (CH), 111.7 (CH_2), 107.3 (C), 73.0 (CH_2), 71.6 (CH_2), 62.9 (C), 53.7 (CH), 52.3 (CH_3), 45.7 (CH), 40.6 (CH), 40.1 (CH_2), 36.9 (CH_2), 35.0 (CH_2), 34.1 (CH_2), 30.2 (C), 22.5 (CH_3), 22.5 (CH_3) ppm. MS (ESI$^+$): m/z = 361 [M + H]$^+$, 378 [M + NH_4]$^+$, 383 [M + Na]$^+$, 399 [M + K]$^+$.

Compound 10d: Brown oil; yield: 58 mg (95%); R_f = 0.63 (Et_2O/petrol ether, 70:30). IR (film): $\tilde{\nu}$ = 2926, 2856, 1726, 1609, 1453, 1370, 1244, 1187, 1027, 909, 732 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.73 (m, 1 H), 4.90 (s, 1 H), 4.81 (s, 1 H), 4.23 (q, J = 7.1 Hz, 2 H), 2.64 (d, J = 1.4 Hz, 2 H), 1.90–2.36 (m, 8 H), 2.31 (dd, J = 13.5, 8.1 Hz, 1 H), 1.72–1.84 (m, 2 H), 1.52–1.68 (m, 4 H), 1.10 (m, 3 H), 1.01 (t, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 216.2 (C), 172.7 (C), 153.7 (C), 136.1 (C), 124.2 (CH), 109.8 (CH_2), 61.6 (CH_2), 57.7 (C), 54.5 (C), 43.5 (CH_2), 41.6 (CH), 37.6 (CH_2), 35.8 (CH_2), 32.4 (CH_2), 32.0 (CH_2), 27.8 (CH_2), 24.6 (CH_2), 23.5 (CH_2), 14.2 (CH_3), 13.2 (CH_3) ppm. MS (ESI$^+$): m/z = 317 [M + H]$^+$, 339 [M + Na]$^+$, 355 [M + K]$^+$.

Compounds **9a**–**c**,**e**–**f**, **10b**,**c**, **11** and **12** were previously fully characterized.[11]

Tosylation of 9e: To a solution of **9e** (dr = 4:1, 37 mg, 0.12 mmol) in chloroform (20 mL) at room temp. were added triethylamine (33 µL, 0.24 mmol), pyridine (19 µL, 0.24 mmol), and tosyl chloride (23 mg, 0.12 mmol), and the mixture was refluxed for 24 h. To the cooled reaction mixture was added dichloromethane, aqueous copper sulfate (5%), saturated ammonium chloride, and brine. The organic layer was separated, the aqueous layer was extracted once with dichloromethane, and the combined organic layers were dried with anhydrous Na_2SO_4, filtered, and concentrated. The crude product was purified by flash chromatography, eluting with AcOEt in petrol ether to give 39 mg (70%) of tosylated **9e** (single isomer from the major isomer of **9e**) as white crystals (after slow evaporation of the eluent) suitable for X-ray analysis. R_f = 0.21 (AcOEt/petrol ether, 40:60); m.p. not determined. IR (film): $\tilde{\nu}$ = 3454, 2954, 2867, 1598, 1470, 1358, 1176, 1107, 963, 909, 837, 733 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.80 (d, J = 8.3 Hz, 2 H), 7.35 (d, J = 8.3 Hz, 2 H), 5.40–5.60 (m, 2 H), 4.06–4.16 (m, 1 H), 4.03 (d, J = 9.5 Hz, 1 H), 3.97 (d, J = 9.5 Hz, 1 H), 3.40 (s, 2 H), 3.37 (d, J = 2.8 Hz, 2 H), 2.44 (s, 3 H), 2.32–2.39 (m, 1 H), 2.26–2.32 (m, 1 H), 2.06–2.26 (m, 7 H), 1.68 (br. s, 1 H), 1.29–1.40 (m, 2 H), 0.95 (s, 3 H), 0.91 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 145.1 (C), 132.8 (C), 130.1 (CH), 130.1 (CH), 128.3 (CH), 128.1 (CH), 128.1 (CH), 126.6 (CH), 107.9 (C), 76.5 (CH_2), 76.5 (CH), 73.0 (CH_2), 71.5 (CH_2), 49.5 (C), 47.3 (CH), 44.9 (CH), 41.9 (CH), 41.2 (CH_2), 35.0 (CH_2), 33.8 (CH_2), 29.5 (CH_2), 30.2 (C), 22.6 (CH_3), 22.5 (CH_3), 21.8 (CH_3) ppm. MS (ESI$^+$): m/z = 463 [M + H]$^+$, 485 [M + Na]$^+$, 501 [M + K]$^+$.

Supporting Information (see footnote on the first page of this article): Copies of ^{1}H and ^{13}C NMR spectra for all new compounds.

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