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Baeyer–Villiger Oxidation of the Bicyclo[2.2.2]octanone System Revisited: Searching for a Modular Construction of Heavily Substituted Cyclohexanes Based on *m*-CPBA Mediated Selective Oxygen Insertion

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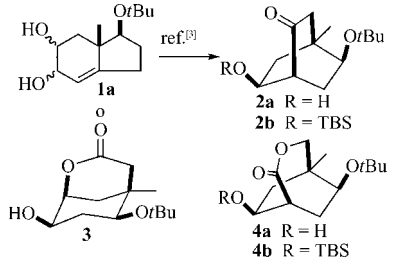
Described herein is the use of Baeyer–Villiger oxidation for the selective insertion of oxygen into a variously substituted bicyclo[2.2.2]octanone system, synthesized by a consecutive domino process. By using the appropriate sequence of steps and starting from common intermediate **2a**, six-membered ring systems with appropriate substituents that could serve as surrogates for several functionalities could be accessed.

Introduction

Recently, a new class of domino transformations[1] was developed in our laboratories through the reaction of bicyclic unsaturated diols, such as **1a** derived from the Hajos–Parrish ketone,[2] with two oxidants (the ecofriendly version) and one base, in a consecutive way.[3] The two oxidants promote the cleavage and ring expansion whereas the base added at the end of the sequence provides the ring system interchange, which leads to high isolated yields of bicyclic[2.2.2]aldol **2a** (Scheme 1). We sought to take advantage of this rapid increase in the molecular complexity in the construction of stereodefined six-membered rings. A preliminary study was thus performed to determine the regiochemistry of the Baeyer–Villiger reaction[4] by varying only one parameter (free or TBS-protected C2-hydroxy group). This established that when **2a** was treated with *m*-CPBA in CH_2Cl_2,[5] product **3** with a migrated bridgehead (electronic control) was isolated as the major bicyclic lactone (through a spontaneous translactonization process) along with methylene migrated (steric control) minor bicyclic lactone **4a** (**3**/**4a** 17:1 ratio). Upon TBS protection of the free hydroxy group to give **2b** and followed by oxidation, the formation of methylene migration product **4b** became competitive with the bridgehead migration product (2.3:1 ratio, respectively); the yield decreased as large amounts of starting material were recovered intact.[6]



Scheme 1.

Reversal of the relative configuration of a quaternary center (C4) was achieved through a three-reaction sequence; domino transformation of **1a**, followed by *m*-CPBA mediated Baeyer–Villiger oxidation of **2a**, and subsequent reductive lactone ring opening to yield 1,2,4,5-tetrasubstituted cyclohexane derivative **5** by C1–C7 bond cleavage (Scheme 2). More recently, heavily functionalized stereopure cyclic systems, which could be used as tridentate ligands **6** (path "RM")[7] or as precursors to the taxoid C-ring **7a**[8] (C1–C2 bond cleavage, MOM = methoxymethyl), were prepared efficiently from a close derivative: conveniently elaborated bicyclic framework **I**.

These results led us to investigate whether the regiochemical outcome could be programmed by performing the Baeyer–Villiger oxidation under conditions favoring any one of the possible openings, as portrayed in Scheme 2. Thus, breaking of the C7–C8 and C1–C7 bonds would enable inversion at the quaternary center, affording compounds of type **5** and **8** whereas breaking of C1–C2 would enable retention at the quaternary center, affording compounds of type **7**. Finally, a C4–C5 type opening through tricyclic orthoester **9** could be viewed as a versatile synthesis of stereopure 1,2,3,4,5-substituted cyclohexane frameworks

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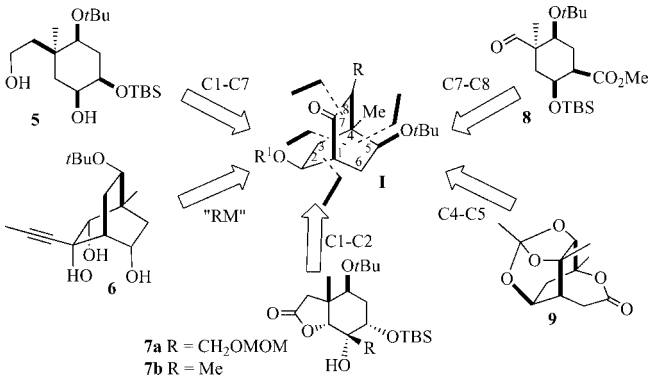


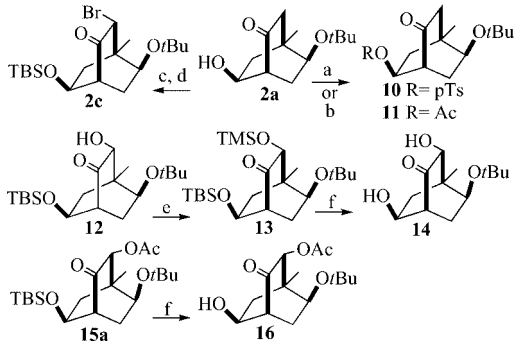
Scheme 2. Routes for practical syntheses of stereopure six-membered ring subunits by applying suitable reaction sequences to conveniently functionalized domino product **I**.

offering regio-, chemo-, and stereoselectivity in further syntheses. Before this methodology could be applied to natural product synthesis, additional studies were needed to probe the regio aspects of the Baeyer–Villiger oxidation of bridged bicyclic aldols of type **I**, which could afford lactones with reasonable control of bridgehead over methylene migration. Opening of the lactones would in turn allow access to configuration reversal/retention at C4. Accordingly, the purpose of this work is to put forward routes that allow construction of cyclohexane building blocks by using Baeyer–Villiger oxidation and subsequent lactone ring opening, starting from easily available bicyclic framework **I** (R = OH, OAc, OTMS, Br; R^1 = H, Ts, Ac, TBS, Scheme 2). We report in this paper the syntheses of selected bicyclic[2.2.2]-octane frameworks derived from bicyclic aldol **2a** and their reactivity pattern.

Results and Discussion

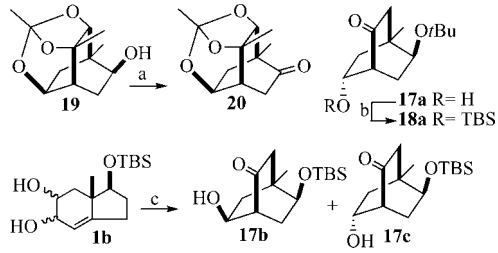
Preparation of the Substrates

The required bicyclic aldol frameworks for this process were readily prepared by functional group interconversion of known compounds **2a**, **12**, **15**, and **19** that were synthesized in our previous work by using consecutive domino reactions as a key step of the sequence along with the atypical ozonolysis for the introduction of the oxygen functionality α to the ketone.[3,7,8] The problem of competitive migratory aptitudes could be reduced to the simple task of preparing α-halogen or α-hydroxy ketones starting from key intermediate **2a**. Furthermore, as *syn* or *anti*-C8 substituents in bicyclo octanones could dictate the migration of the methylene unit in preference to the bridgehead carbon, we planned to use a bulky protecting group at C2 and oxo-substitution at C8 to divert the reaction course in a more elaborate fashion. The directing effect of the substituent α to the carbonyl group was first targeted in an attempt to see whether the Baeyer–Villiger reaction of an α-bromo ketone[9] would permit regiospecific ring opening. To this end, conversion of bicyclic aldol **2a** to its α-halogenated derivative **2c** was accomplished by a three-step sequence in 90% overall yield. Protection of **2a** by treatment with *tert*-butyldimethylsilyl chloride (TBSCl, imidazole, DMF, 0 °C) followed by silyl enol ether formation (TMSOTf, collidine, CH_2Cl_2, 0 °C, 2 h) and treatment of the latter with NBS (THF, 0 °C) afforded **2c** as a single diastereomer (stereochemistry as depicted in Scheme 3). On the other hand, the cation-stabilizing effect of the lone pair of electrons on oxygen would increase the relative migratory aptitude of the attached carbon.[10] To verify this hypothesis, acyloins **12**–**16** were synthesized according to our previous work. Starting from known **15a**, its free hydroxy derivative **16** was prepared by desilylation with tetra-*n*-butylammonium fluoride (TBAF, THF, 0 °C, 90%).



Scheme 3. (a) *p*-TsCl, py, DMAP, 0 °C to 25 °C; (b) Ac_2O, py, DMAP, 0 °C, 1 h 30 min; (c) TBSCl, DMF/imidazole, 0 °C to 25 °C, 16 h; (d) (i) TMSOTf, collidine, PhMe, 25 °C; (ii) NBS, THF, 0 °C; (e) TMS/imidazole, CH_2Cl_2, 0 °C; (f) TBAF, THF, 0 °C.

Required orthoester **20** was readily prepared by Dess–Martin oxidation of known alcohol **19** (Scheme 4). The one-pot synthesis of **17b**, obtained along with its α-OH epimer **17c** from **1b** (71% combined isolated yield, 4:1 ratio,[11] respectively) was identical with our published synthesis of bicyclic aldol **2a**, save that the *t*Bu protecting group was substituted with TBS (Scheme 4).

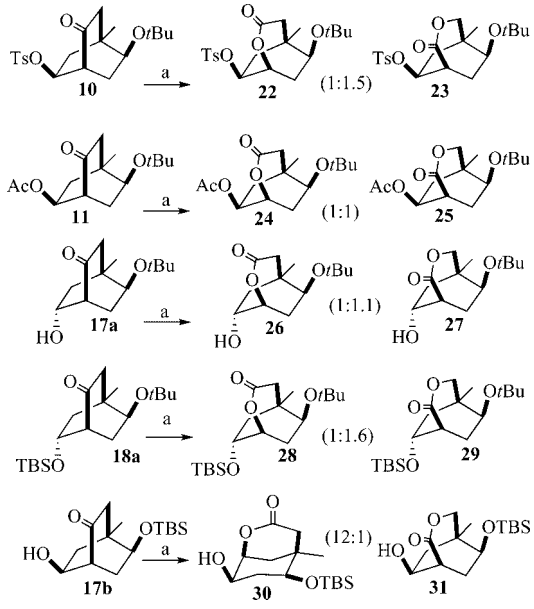


Scheme 4. (a) Dess–Martin periodinane, CH_2Cl_2, py, 25 °C, 0.5 h; (b) TBSCl, DMF/imidazole, 0 °C to 25 °C, 16 h; (c) 2.4 equiv. $Pb(OAc)_4$, PhMe then K_2CO_3/MeOH, H_2O, 25 °C.

The Influence of Substituents on the Regiocontrol of Oxygen Insertion

With the required substrates in hand, inspection of the regiochemical outcome for oxygen insertion was carried out. To this end, the bicyclic aldols thus obtained were converted into their corresponding lactones by exposure to Baeyer–Villiger oxidation, carried out with an excess

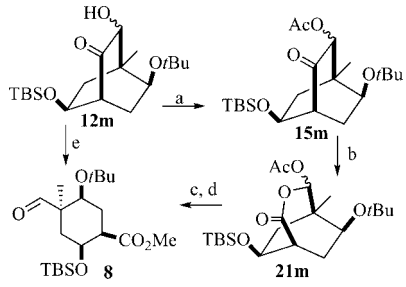
amount of *m*-chloroperbenzoic acid (*m*-CPBA) in sodium hydrogencarbonate buffered dichloromethane, at room temperature. To have a better comparison of the results we chose to stay with the same peracid rather than complicating comparisons by using various oxidants.[12] In every case investigated, the regiochemistry of the Baeyer–Villiger reaction was unambiguously confirmed by long-range heteronuclear couplings observed in the HMBC spectra. Ratios of the bridgehead- to methylene-migrated lactones were determined by SiO_2 separation and, where possible, by comparison of the integrated areas for the methylene protons adjacent to the carbonyl group in the bridgehead-migrated lactones to the oxygen in the methylene-migrated lactones and the bridgehead protons in both cases. It was anticipated that the regiochemistry of the Baeyer–Villiger oxidation of **10** and **11** could, in principle, be a function of the inductive effect of the C2 substituent (OAc, OTs) rather than a steric effect as for **2b**. The *m*-CPBA oxidation of tosylate **10** and acetate **11** required long reaction times (4 d) for lactone formation and furnished significantly lower yields of the bridgehead- and methylene-migrated products as inseparable mixtures. Thus, **10** afforded **22** and **23** in 24% combined yield (93% based on recovery of starting material) and 1:1.5 ratio, whereas **11** gave **24** and **25** in 37% combined yield (91% based on recovery of starting material) and 1:1 ratio (Scheme 5).



Scheme 5. Reagents and conditions: 3 equiv. *m*-CPBA, 1.2 equiv. $NaHCO_3$, CH_2Cl_2, 25 °C.

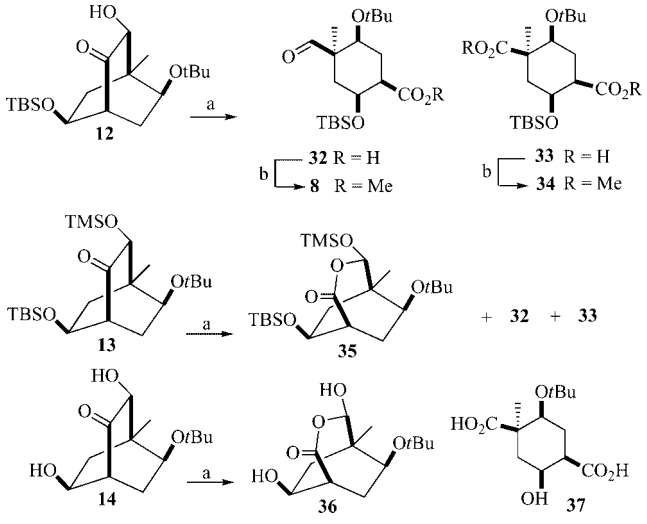
The tendency for methylene group migration is increased (relative to **2a**)[13] on introducing an electron-withdrawing group at C2, although the latter may not be solely responsible for the regioselectivity observed. The electron demand of the group at this position is obviously transmitted to C1, which is then less able to support a build-up of positive charge as required for the migrating group in the rearrangement step, yet the roles played by electronic and steric factors remain unclear. Substrates with a free α-hydroxy group offer very poor selectivity, showing very little preference for methylene migration. Indeed, the presence or the absence of the bulky protecting group in **18a** and **17a**, respectively, do not change the reaction outcome (hydrogen bonding with the free α-hydroxy group being unlikely). We did not detect a similar regioreversal as in **2b** versus **2a** during the oxidation of *tert*-butyldimethylsilyl protected bicyclic aldol **18a** (α-OTBS), derived from corresponding alcohol **17a** (α-OH). When the latter, possessing a free α-hydroxy group at C2, was subjected to Baeyer–Villiger oxidation (4 h), lactone **26** was produced accompanied by its regioisomer **27**, in 88% isolated yield and 1:1.1 ratio. Subjected to the same Baeyer–Villiger conditions, **18a** afforded a 48% isolated yield of **29** together with 30% of **28** after 15 h of stirring at room temperature. In both cases, the major lactone arises from migration of the methylene carbon as opposed to the carbon at the bridgehead position. Thus, upon protection of the free β-hydroxy group of **2a**, a 2.3:1 preference for methylene migration was observed; the sense of bridgehead versus methylene migration remained unchanged with regard to the migration preference although the ratio slightly increased in favor of methylene migration for the Baeyer–Villiger oxidation of **18a** (**28**/**29**, 1:1.6).

A change in the protecting group at C5, *tert*-butyldimethylsilyl (TBS) instead of *t*Bu, did not have a significant influence in controlling the outcome of the Baeyer–Villiger reaction, since a 12:1 ratio of bridgehead versus methylene migration was obtained, whereas yields remained modest (slightly above 50% isolated yield). Thus, **17b** gave mainly lactone **30** (49%) resulting from bridgehead migration and subsequent translactonization on treatment with *m*-CPBA, but 4% of an isomer, lactone **31**, was also detected though not isolated pure. Our next experiment focused on the course of the Baeyer–Villiger oxidation of acyloin **15m** (C8 epimeric mixture), obtained from known **12m** by acetylation.[7] Thus, upon treatment of **15m** with *m*-CPBA (15 h, 25 °C), a single product, **21m**, was obtained in over 75% yield. This material was subjected to lactone ring opening (K_2CO_3, MeOH, room temp. 1.5 h) and subsequent esterification ($TMSCHN_2$, Et_2O, MeOH, 0 °C, 93% two steps) and compared with the oxidative fission of **12m** [$Pb(OAc)_4$, toluene/methanol, 0 °C, 90% isolated yield]; both afforded cleanly aldehyde ester **8** (Scheme 6).

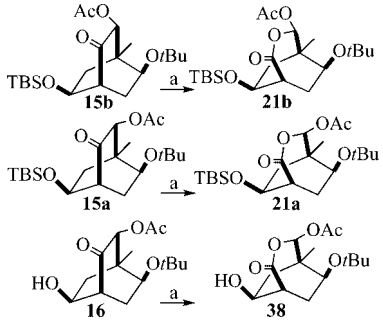


Scheme 6. (a) Ac_2O, py, DMAP, 0 °C, 1 h 30 min; (b) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, 25 °C; (c) K_2CO_3, MeOH, 25 °C 1 h 30 min; (d) $TMSCHN_2$, Et_2O, MeOH, 0 °C; (e) $Pb(OAc)_4$, toluene, MeOH, 0 °C.

This result establishes firmly the course of the reaction to be oxygen insertion α to acetoxy substituent, which has taken precedence over the migration of a tertiary group (bridgehead migration). The reaction of acetoxy–acyloin **15m**, although performed on an epimeric mixture, appears to have potential utility since oxygen insertion is regioselective. By investigating migration preferences, parallel studies to those just detailed on **12m** (epimeric mixture) were next performed to examine the migrating preferences of stereodefined acyloins **12**–**16**, with the aim of ultimately ensuring their conversion to heavily substituted cyclohexanes (Schemes 7 and 8). Bicyclic framework **12**, which was obtained as the major isomer following atypical ozonolysis was treated with *m*-CBPA (1.5 h) to afford a 79% combined yield of **32** and **33**, both arising from cleavage, in a 1.7:1 ratio, respectively. Esterification ($TMSCHN_2$ Et_2O, MeOH, 0 °C, 93%) of **32** gave **8** and similarly **33** gave **34** (Scheme 7). In a complementary fashion, bis(silyl)-protected acyloin **13** (22 h), as well as free acyloin **14** (3.5 h), upon Baeyer–Villiger oxidation afforded three or two products, respectively, but in both cases only the α oxygen bearing atom migrated to oxygen, (**32**, **33** and **37** being the corresponding ring-opened derivatives).[14]



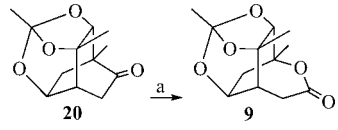
Scheme 7. Reagents and conditions: (a) 3 equiv. *m*-CPBA, 1.2 equiv. $NaHCO_3$, CH_2Cl_2, 25 °C. (b) $TMSCHN_2$, Et_2O, MeOH, 0 °C to 25 °C.



Scheme 8. Reagents and conditions: (a) 3 equiv. *m*-CPBA, 1.2 equiv. $NaHCO_3$, CH_2Cl_2, 25 °C.

On the other hand, Baeyer–Villiger oxidation of **15b** proceeded with exclusive migration of the acetoxy-substituted carbon to afford lactone **21b** (2 h, 95% isolated yield, single product) as depicted in Scheme 8. An acetoxy group at C8 placed *syn* to the O*t*Bu group appears to have an unusually large rate-retarding effect. Thus, the Baeyer–Villiger reaction of **15a** was much slower (25 h) and gave lactone **21a** along with unreacted starting material (56% isolated yield, 83% based on recovered starting material). Accordingly, insofar as migrating preferences are concerned, it is apparent that both **15a** and **15b** behave in a manner completely analogous to **15m** in their reaction with *m*-CPBA. Both bicyclic frameworks gave single lactones **21a** and **21b**, respectively, derived from Baeyer–Villiger oxidation involving exclusive migration of the oxygenated carbon. However, there is a noteworthy rate- and yield-lowering effect on **15a**, indicating that the reaction course is affected by the configuration at C8. When bicyclic aldol **16** possessing a free α-hydroxy group at C2 along with a *syn* O*t*Bu acetoxy group at C8 was subjected to Baeyer–Villiger oxidation, lactone **38** was produced in 87% isolated yield, after 15 h at room temperature as the sole reaction product (interestingly, bridgehead migration was totally absent). Lactones **21a**, **21b**, **35**, **36** and **38** were produced uncontaminated by their regioisomer (Schemes 7 and 8), as confirmed by NMR spectroscopic analyses.

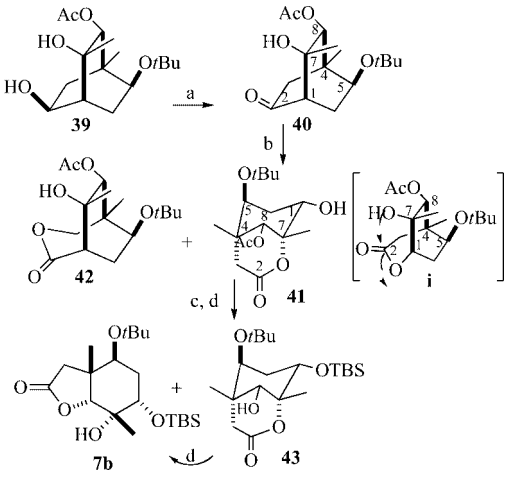
Two additional substrates, issued from the common bicyclic[2.2.2]aldol framework **2a** were straightforwardly synthesized from known precursors **19** and **39**, orthoester **20** (Scheme 9) and bicyclic aldol **40** (Scheme 10), respectively, and subjected to Baeyer–Villiger conditions. It was expected that oxidation of these substrates would proceed with bridgehead migration and subsequent lactone ring opening would provide pentasubstituted cyclohexanes with retention of configuration (relative configuration of the angular methyl group and O*t*Bu as in **1a**) at the quaternary center. Baeyer–Villiger oxidation of **20** (3 equiv. *m*-CPBA, 1.2 equiv. $NaHCO_3$, CH_2Cl_2, 25 °C, 3 d) afforded **9**, proceeding almost exclusively through bridgehead migration in 88% isolated yield along with recovered starting material (8%), whereas methylene migrated lactone could not be detected (Scheme 9).



Scheme 9. (a) 3 equiv. *m*-CPBA, 1.2 equiv. $NaHCO_3$, CH_2Cl_2, 25 °C, 3 d.

Efforts to obtain desired[15] bicyclo[3.3.1]nonane **41** along the lines described above were less gratifying owing to a modest regioselectivity in the Baeyer–Villiger oxidation (3 equiv. *m*-CPBA, 1.2 equiv. $NaHCO_3$, CH_2Cl_2, 25 °C, 20 h) of bicyclic aldol **40**. However, methylene migrated isomer comprised a considerably smaller proportion of the crude product than in the aforementioned cases (Scheme 5). Resulting lactones **41** (following an in situ translactoni-

zation via **i**, Scheme 10) and **42** (67% combined yield of **41**, **42** in 4.4:1 ratio) were obtained pure along with recovered **40** (30%).



Scheme 10. (a) Dess–Martin periodinane, CH_2Cl_2, 25 °C; (b) 3 equiv. *m*-CPBA, 1.2 equiv. $NaHCO_3$, CH_2Cl_2, 25 °C, 20 h; (c) TBSCl, DMF/imidazole, 0 °C to 25 °C, 16 h; (d) K_2CO_3, $MeOH/H_2O$, 25 °C.

The illustrated configurations at the newly installed stereogenic centers within these products follow from extensive NMR spectroscopic studies and from an X-ray crystallographic study on **43** (see Supporting Information), a derivative of **41**. The latter was first silyl-protected at C1 (TBSCl, DMF/imidazole, 0 to 25 °C, 16 h, 92%) then saponified (K_2CO_3, $MeOH/H_2O$, 25 °C) to afford crystalline **43** along with its translactonized counterpart **7b** (90% yield, ca. 1:1), which is indeed the ultimate target, being a precursor of heavily functionalized six-membered ring system. We have experimental evidence that bridged bicyclic lactone **43** is formed initially but rapidly converts to fused bicyclic lactone **7b** by an intramolecular translactonization to give a sterically less-crowded product (Scheme 9). Pure **43**, subjected to the same mild base treatment (K_2CO_3, $MeOH/H_2O$, 25 °C) was smoothly converted into **7b**. Finally, attempted Baeyer–Villiger oxidations (using an excess amount of reagent and prolonged reaction times) of **2c** failed, presumably due to the electron withdrawing effect of the α halogen, which completely suppressed the migration of the carbon bearing it.[16]

Conclusions

With the ultimate aim of selectively preparing heavily functionalized cyclohexane derivatives, we inspected the regiochemical outcomes for the Baeyer–Villiger oxidation of variously substituted bicyclo[2.2.2]octanone system **I** (Scheme 2). Our key incentive for this work was to examine whether the choice of the opening position would afford practical control of the relative configuration at the quaternary center in bridgehead position C4. To summarize, under the selected experimental conditions we observed that: (1) In the absence of C8 substitution, bridgehead migration was favored on free C2β-hydroxy-containing substrates whereas on those having the C2β-hydroxy group protected, methylene migration increased significantly. A tosyloxy or acetoxy group on C2 appears to have an unusually large rate-retarding effect. Regioselectivity was insignificant for the former, nil for the latter and the yield decreased as large amounts of starting material were recovered intact. (2) Substrates with a free C2α-hydroxy group offered a poor selectivity, showing very little preference for methylene migration. (3) The regiochemical outcome was completely reversed (whereas it was unbiased to the configuration of the C8 carbon) with C8 acyloins (**I**, R = OH, OTMS, OAc) where only hydroxy-, silyloxy- and acetoxy-substituted carbon migrates in preference to the tertiary bridgehead carbon.

Given the fact that the lactones thus obtained are readily amenable to either hydrolytic or reductive opening, this allows easy access to 1, 2, 4, 5- and 1, 2, 3, 4, 5-substituted stereodefined cyclohexanes. Thus, by using the consecutive domino reaction discovered in our laboratory, and proceeding as portrayed in Scheme 2, we can target the synthesis of either type **5** or **8** cyclohexanes (C1–C7 and C7–C8 cleavage, respectively) with inversion or those accessible from **7** and **9** (C1–C2 and C4–C5 cleavage, respectively), with retention of configuration at the quaternary center, respectively.

Experimental Section

General Remarks: Commercially available *m*-CBPA (Aldrich) was purified by washing with pH 7.4 phosphate buffer and drying under reduced pressure. "Usual workup" means washing of the organic layer with brine, drying on anhydrous $MgSO_4$, and evaporating in vacuo with a rotary evaporator at aspirator pressure. Melting points are uncorrected. IR spectra were recorded with an FTIR instrument through NaCl cell windows and absorptions are given in cm^{-1}. NMR spectra were run in $CDCl_3$ unless otherwise noted. Experimental evidence favoring the structures investigated came from a comprehensive range of ^1H and ^{13}C NMR spectroscopic data (500/125 and 300/75 MHz respectively, 1D and 2D experiments) and corroborated by spatial proximity (n.O.e) studies using 1 and D techniques. ^1H chemical shifts are expressed in ppm downfield from TMS using the residual nondeuterated solvent as internal standard ($CDCl_3$, ^1H, 7.26 ppm). ^{13}C chemical shifts are reported relative to $CDCl_3$ triplet centered at δ = 77.0 ppm. Mass spectra acquired in the positive ion mode under electron spray ionization (ES+) using a mobile phase of methanol, will be abbreviated as ESIMS (MeOH). HR will be added for the high resolution mass measurements (HRESIMS).

CCDC-620081 (**43**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Typical Procedure for Baeyer–Villiger Oxidation: Sodium hydrogen carbonate (0.12 mmol) and *m*-CPBA (0.3 mmol) were added to the appropriate ketone (0.1 mmol) in dichloromethane (1 mL) at 0 °C. The mixture was stirred at room temp (for approximately 17 h or as indicated, TLC monitoring). The crude reaction mixture was diluted with dichloromethane and filtered through a plug of Celite. The excess peracid was decomposed by washing with aqueous 5% sodium sulfite. Finally the organic phase was washed with sat. $NaHCO_3$, and worked up as usual.

Baeyer–Villiger Oxidation of the Substrates

6-(*tert*-Butyldimethylsilanyloxy)-8-hydroxy-5-methyl-2-oxabicyclo-[3.3.1]nonan-3-one (30): Starting from **17b** (74 mg, 0.314 mmol) and using the general procedure, **30** (46.5 mg, 49%) was obtained, after stirring at room temp. for 14 h (silica gel chromatography, heptane/EtOAc, 1:1), along with impure **31** (5.4 mg, 4%) and recovered starting material (11 mg, 14.8%). $[a]_D^{20}$ = 65 (c = 1.0, $CHCl_3$). M.p. 188–189 °C (CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.04 (s, 3 H), 0.06 (s, 3 H), 0.87 (s, 9 H), 0.96 (s, 3 H), 1.29 (ddd, J = 11.6, 11.6, 13.7 Hz, 1 H), 1.46 (ddd, J = 1.7, 2.2, 14.6 Hz, 1 H), 1.94 (dd, J = 4.6, 14.6 Hz, 1 H), 2.02 (dd, J = 0.9, 19.0 Hz, 1 H), 2.17 (dddd, J = 1.0, 5.1, 5.1, 13.7 Hz, 1 H), 2.25 (br. s, 1 H), 2.94 (dd, J = 2.4, 19.0 Hz, 1 H), 3.37 (ddd, J = 0.7, 5.1, 11.4 Hz, 1 H), 3.65 (ddd, J = 2.4, 5.2, 11.9 Hz, 1 H), 4.61 (dddd, J = 1.0, 1.7, 2.4, 4.6 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = –4.8, –3.8, 18.1, 25.9, 26.6, 33.9, 34.8, 36.2, 37.2, 70.6, 73.8, 78.5, 171.6 ppm. IR (film): 1698, 1313, 1249, 1215, 1130, 993, 835, 775 cm^{-1}. ESIMS (MeOH): m/z (%) = 323.1 (100) $[M + Na]^+$. HRESIMS (MeOH): calcd. for $C_{15}H_{28}O_4NaSi$ 323.1655; found 323.1644. $C_{15}H_{28}O_4Si$ (300.46): calcd. C 59.96, H 9.39; found C 60.04, H 9.46.

8-*tert*-Butoxy-6-(*tert*-butyldimethylsilanyloxy)-1-methyl-4-oxo-3-oxabicyclo[2.2.2]non-2-yl Acetate (21a): Starting from **15a** (37 mg, 0.09 mmol) and using the general procedure, **21a** (21.5 mg, 56%) was obtained, after stirring at room temp. for 25 h (silica gel chromatography, heptane/EtOAc, 20:1 to 10:1), along with unreacted starting material **15a** (9.6 mg, 26%). $[a]_D^{20}$ = +13 (c = 0.7, $CHCl_3$). M.p. 146–147 °C (CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.00 (2 s, 6 H), 0.81 (s, 9 H), 0.98 (s, 3 H), 1.09 (s, 9 H), 1.79 (m, 2 H), 2.02 (s, 3 H), 2.04–2.20 (m, 2 H), 2.97 (m, 1 H), 3.38 (t, J = 8.0 Hz, 1 H), 3.99 (m, 1 H), 6.13 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = –4.9, –4.8, 17.9, 20.9, 24.6, 25.6 (3 C), 28.8 (3 C), 31.3, 41.6, 43.6, 49.3, 65.6, 70.1, 73.3, 97.9, 169.1, 172.2 ppm. IR (film): $\tilde{\nu}$ = 2960, 2858, 1752, 1363, 1016 cm^{-1}. ESIMS (MeOH): m/z (%) = 437.2 (100) $[M + Na]^+$. HRESIMS: calcd. for $C_{21}H_{38}O_6SiNa$ 437.2335; found 437.2328. $C_{21}H_{38}O_6Si$ (414.24): calcd. C 60.83, H 9.24; found C 60.69, H 9.24.

8-*tert*-Butoxy-6-(*tert*-butyldimethylsilanyloxy)-1-methyl-4-oxo-3-oxabicyclo[3.2.2]non-2-yl Acetate (21b): Starting from **15b** (110 mg, 0.27 mmol) and using the general procedure, **21b** (106 mg, 95%) was obtained, after stirring at room temp. for 2 h as a single product (silica gel chromatography, heptane/EtOAc, 20:1 to 10:1). $[a]_D^{20}$ = +100 (c = 1.2, $CHCl_3$). M.p. 94–96 °C (CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.07 (2 s, 6 H), 0.89 (s, 9 H), 0.99 (s, 3 H), 1.17 (s, 9 H), 1.66 (dd, J = 8.6, 15.2 Hz, 1 H), 1.89 (dt, J = 3.0, 15.4 Hz, 1 H), 1.97–2.09 (m, 2 H), 2.10 (s, 3 H), 3.06 (m, 1 H), 3.51 (dd, J = 3.5, 8.7 Hz, 1 H), 3.97 (m, 1 H), 6.42 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = –4.9 (2 C), 17.9, 21.0, 24.9, 25.6 (3 C), 28.7 (3 C), 32.2, 37.5, 42.3, 48.9, 66.0, 70.3, 74.0, 94.7, 169.1, 171.5 ppm. IR (film): $\tilde{\nu}$ = 2930, 2857, 1749, 1225, 1173 cm^{-1}. ESIMS (MeOH): m/z (%) = 437.2 (100) $[M + Na]^+$, 453.2 (12) $[M + K]^+$. HRESIMS: calcd. for $C_{21}H_{38}O_6NaSi$ 437.2335; found 437.2339. $C_{21}H_{38}O_6Si$ (414.24): calcd. C 60.83, H 9.24; found C 60.59, H 9.17.

9-*tert*-Butoxy-5-methyl-3-oxo-2-oxabicyclo[3.2.2]non-7-yl Toluene-4-sulfonate (23), 8-*tert*-Butoxy-1-methyl-4-oxo-3-oxabicyclo[3.2.2]non-6-yl Toluene-4-sulfonate (22): Starting from **10** (49 mg, 0.12 mmol) and using the general procedure, **22** and **23** (11.5 mg) were obtained as an inseparable mixture, after stirring at room temp. for 4 d in 24% combined yield and 1:1.5 ratio (silica gel chromatography, heptane/EtOAc, 10:1 to 3:1), along with unreacted starting material **10** (33.8 mg, 69%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.89 (s, 3 H, Me′), 0.90 (s, 3 H, Me), 1.10 (s, 18 H, tBu), 1.68 (ddd, J = 1.7, 5.2, 15.3 Hz, 1 H, H_6), 1.75 (dd, J = 6.1, 15.4 Hz, 1 H, H_7′), 2.00–2.16 (m, 5 H, H_9′, H_7′, H_6, H_8), 2.30 (ddd, J = 5.7, 8.6, 16.2 Hz, 1 H, H_9′), 2.39 (dd, J = 1.5, 18.7 Hz, 1 H, H_4), 2.44 (s, 3 H, Ts′), 2.45 (s, 3 H, Ts), 2.98 (ddd, J = 1.7, 5.4, 6.6 Hz, 1 H, H_5′), 3.12 (dd, J = 2.6, 18.7 Hz, 1 H, H_4), 3.38–3.44 (m, 2 H, H_9, H_8′), 3.71 (dd, J = 1.2, 11.9 Hz, 1 H, H_2′), 4.35 (ddd, J = 1.8, 3.2, 5.6 Hz, 1 H, H_1), 4.41 (dd, J = 1.4, 11.9 Hz, 1 H, H_2′), 4.78–4.87 (m, 2 H, H_7, H_6′), 7.34 (d, J = 8.3 Hz, 4 H, Ts), 7.79 (d, J = 8.3 Hz, 4 H, Ts) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.2 (Me′), 27.4 (Me), 27.7 (2 Ac), 28.7 (6 C, 2 tBu), 32.2 (C9′), 35.0 (C5), 37.3 (C8), 38.4 (C7′), 38.8 (C6), 39.5 (C1′), 43.3 (C4), 46.0 (C5′), 68.7 (C8′), 69.1 (C9), 73.3 (C2), 73.7 (tBu′), 74.0 (tBu), 74.3 (C1), 74.8 (C6′), 75.2 (C7), 127.8 (4 C, Ts), 129.9 (4 C, Ts), 133.6 (2 C, Ts), 145.1 (2 C, Ts), 171.5 (2 C, C3, C4′) ppm. IR (film): $\tilde{\nu}$ = 2963, 2927, 2873, 2856, 1782, 1731, 1598, 1365, 1190, 1176, 882 cm^{-1}. ESIMS (MeOH): m/z (%) = 419.1 (100) $[M + Na]^+$. HRESIMS: calcd. for $C_{20}H_{28}O_6SNa$ 419.1504; found 419.1495. $C_{20}H_{28}O_6S$ (396.16): calcd. C 60.58, H 7.12, S 8.09; found C 64.09, H 8.06, S 5.68.

9-*tert*-Butoxy-5-methyl-3-oxo-2-oxabicyclo[3.2.2]non-7-yl Acetate 24 and 8-*tert*-Butoxy-1-methyl-4-oxo-3-oxabicyclo[3.2.2]non-6-yl Acetate (25): Starting from **11** (43 mg, 0.16 mmol) and using the general procedure, **24** and **25** (16.6 mg) were obtained as an inseparable mixture, after stirring at room temp. for 4 d in 37% combined yield and 1:1 ratio (silica gel chromatography, heptane/EtOAc, 10:1 to 3:1), along with recovered starting material **11** (23.2 mg, 54%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.84 (s, 3 H, Me), 0.88 (s, 3 H, Me′), 1.10 (s, 18 H, tBu), 1.68 (dd, J = 5.7, 14.9 Hz, 1 H, H_6), 1.75 (dd, J = 5.7, 15.0 Hz, 1 H, H_7′), 1.85 (ddd, J = 1.4, 5.6, 15.3 Hz, 1 H, H_9′), 1.92–2.12 (m, 3 H, H_8, H_7, H_7′), 1.99 (s, 3 H, Ac), 2.02 (s, 3 H, Ac), 2.17 (ddd, J = 6.9, 8.5, 15.3 Hz, 1 H, H_9′), 2.27 (ddd, J = 5.4, 8.6, 16.2 Hz, 1 H, H_8), 2.37 (dd, J = 1.4, 18.6 Hz, 1 H, H_4), 3.03 (ddd, J = 1.5, 5.1, 6.9 Hz, 1 H, H_5′), 3.10 (dd, J = 2.7, 18.6 Hz, 1 H, H_4), 3.41 (m, 2 H, H_9, H_8′), 3.64 (dd, J = 1.2, 11.9 Hz, 1 H, H_2′), 4.41 (dd, J = 1.6, 11.9 Hz, 1 H, H_2′), 4.44 (ddd, J = 1.9, 3.5, 5.4 Hz, 1 H, H_1), 4.89 (ddd, J = 3.4, 5.7, 9.6 Hz, 1 H, H_7), 4.95 (dt, J = 5.4, 9.2 Hz, 1 H, H_6′) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.0 (Ac), 21.1 (Ac), 24.3 (Me′), 27.6 (Me), 28.8 (6 C, 2 tBu), 32.0 (C9′), 34.8 (C5), 37.2 (C8), 37.6 (C7′), 38.2 (C6), 39.4 (C1′), 43.4 (C4), 45.3 (C5′), 67.9 (C6′), 68.9 (2 C, C9, C8′), 69.5 (C7), 73.5 (C2′), 73.7 (tBu), 73.8 (tBu′), 74.3 (C1), 170.5 (Ac), 170.6 (Ac), 172.3 (C3), 173.0 (C4′) ppm. IR (film): $\tilde{\nu}$ = 2975, 1738, 1731, 1366, 1242, 1049 cm^{-1}. ESIMS (MeOH): m/z (%) = 307.1 (100) $[M + Na]^+$. HRESIMS: calcd. for $C_{15}H_{24}O_5Na$ 307.1521; found 307.1505. $C_{15}H_{24}O_5$ (284.16): calcd. C 63.36, H 8.51; found C 63.61, H 8.45

6-*tert*-Butoxy-8-hydroxy-5-methyl-2-oxabicyclo[3.2.2]nonan-3-one (26) and 6-*tert*-Butoxy-8-hydroxy-5-methyl-3-oxabicyclo[3.2.2]-nonan-2-one (27): Starting from **17a** (40 mg, 0.17 mmol) and using the general procedure bridgehead migrated **26** (17.2 mg) and methylene migrated **27** (18.8 mg) were obtained in 88% combined yield and 1:1.1 ratio after stirring at room temp. for 4 h (silica gel chromatography, heptane/EtOAc, 2:1 to 1.5:1). Data for **26**: $[a]_D^{20}$ = +28 (c = 0.8, $CHCl_3$). M.p. 86–88 °C (heptane). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.95 (s, 3 H), 1.18 (s, 9 H), 1.45 (ddd, J = 2.4, 5.0, 14.7 Hz, 1 H), 2.03 (m, 1 H), 2.18 (dd, J = 8.1, 14.7 Hz, 1 H), 2.31 (dd, J = 1.1, 18.5 Hz, 1 H), 2.48 (ddd, J = 4.3, 8.5, 15.8 Hz, 1 H), 3.01 (dd, J = 2.5, 18.5 Hz, 1 H), 3.64 (dd, J = 2.9, 8.5 Hz, 1 H), 4.29 (m, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.9, 28.8 (3 C), 34.4, 34.5, 42.0, 43.3, 67.1, 70.5, 73.7, 78.0, 173.9 ppm. IR (film): $\tilde{\nu}$ = 3394, 2975, 2929, 1708, 1390, 1067 cm^{-1}. ESIMS (MeOH): m/z (%) = 243.2 (100) $[M + H]^+$, 265.2 (14) $[M + Na]^+$, 281.1 (8) $[M + K]^+$. HRESIMS: calcd. for $C_{13}H_{22}O_4Na$ m/z

265.1416, found: 265.1407. $C_{13}H_{22}O_4 \cdot 0.1H_2O$ (242.15): calcd. C 63.96, H 9.17; found C 63.99, H 9.19. Data for **27**: $[\alpha]_D^{20}$ = +63 (*c* = 1.1, $CHCl_3$). M.p. 141–142 °C (heptane). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.89 (s, 3 H), 1.18 (s, 9 H), 1.58 (ddd, *J* = 1.5, 2.8, 15.2 Hz, 1 H), 1.80 (dd, *J* = 5.3, 14.9 Hz, 1 H), 2.20 (dd, *J* = 8.0, 15.2 Hz, 1 H), 2.43 (ddd, *J* = 6.8, 8.2, 14.9 Hz, 1 H), 2.93 (d, *J* = 6.8 Hz, 1 H), 3.34 (b, 1 H), 3.61 (dd, *J* = 1.3, 11.8 Hz, 1 H), 3.72 (ddd, *J* = 1.3, 5.3, 8.2 Hz, 1 H), 4.29 (dt, *J* = 2.8, 8.0 Hz, 1 H), 4.51 (dd, *J* = 1.5, 11.8 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.3, 28.8 (3 C), 29.8, 37.7, 41.1, 48.6, 64.8, 69.1, 73.4, 74.1, 174.5 ppm. IR (film): $\tilde{\nu}$ = 3383, 2970, 2930, 1719, 1195, 1075 cm^{-1}. ESIMS (MeOH): *m*/*z* (%) = 243.1 (4) $[M + H]^+$, 265.2 (100) $[M + Na]^+$, 281.1 (8) $[M + K]^+$. HRESIMS: calcd. for $C_{13}H_{22}O_4Na$ 265.1416; found 265.1411. $C_{13}H_{22}O_4 \cdot 0.15H_2O$ (242.15): calcd. C 63.73, H 9.17; found C 63.99, H 8.99.

9-*tert*-Butoxy-7-(*tert*-butyldimethylsilyloxy)-5-methyl-2-oxabicyclo-[3.2.2]nonan-3-one (28) and 9-*tert*-Butoxy-7-(*tert*-butyldimethylsilyloxy)-5-methyl-3-oxabicyclo[3.2.2]nonan-2-one (29): Starting from TBS-protected bicyclic aldol **18a** (50 mg, 0.14 mmol) and using the general procedure, **28** (15.6 mg, 30%) and **29** (25 mg, 48%) were obtained after stirring at room temp. for 15 h (silica gel chromatography, heptane/EtOAc, 5:1 to EtOAc). Data for **28**: Yellow oil. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.05 (s, 3 H), 0.07 (s, 3 H), 0.88 (s, 9 H), 0.91 (s, 3 H), 1.16 (s, 9 H), 146 (dd, *J* = 2.1, 14.8 Hz, 1 H), 1.94 (dd, *J* = 3.3, 14.3 Hz, 1 H), 2.12 (dd, *J* = 7.5, 14.7 Hz, 1 H), 2.26 (d, *J* = 18.5 Hz, 1 H), 2.48 (ddd, *J* = 5.3, 8.5, 15.7 Hz, 1 H), 3.07 (dd, *J* = 2.7, 18.5 Hz, 1 H), 3.67 (ddd, *J* = 1.7, 5.0, 8.5 Hz, 1 H), 4.17 (m, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = –4.9, –4.8, 17.8, 25.6 (3 C), 28.0 (3 C), 28.8, 34.3, 35.2, 43.4, 43.5, 67.3, 70.0, 73.4, 77.5, 172.4 ppm. IR (film): $\tilde{\nu}$ = 2953, 2928, 2855, 1730, 1471, 1462, 1388, 1377, 1363, 1252, 1190, 1106, 1083, 1039, 835 cm^{-1}. ESIMS (MeOH): *m*/*z* (%) = 379.2 (100) $[M + Na]^+$. HRESIMS: calcd. for $C_{19}H_{36}O_4NaSi$ 379.2281; found 379.2310. $C_{19}H_{36}O_4Si$ (356.23): calcd. C 64.00, H 10.18; found C 63.87, H 10.13. Data for **29**: Yellow oil. $[\alpha]_D^{20}$ = +65 (*c* = 1.0, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 0.05 (s, 3 H), 0.06 (s, 3 H), 0.88 (s, 3 H), 0.89 (s, 9 H), 1.16 (s, 9 H), 1.52 (dd, *J* = 1.3, 14.9 Hz, 1 H), 1.74 (dd, *J* = 5.9, 14.6 Hz, 1 H), 2.16 (dd, *J* = 7.2, 14.9 Hz, 1 H), 2.35 (m, 1 H), 2.87 (ddd, *J* = 1.7, 3.5, 7.1 Hz, 1 H), 3.53 (dd, *J* = 1.5, 11.8 Hz, 1 H), 3.78 (ddd, *J* = 1.5, 6.2, 8.0 Hz, 1 H), 4.18 (m, 1 H), 4.53 (dd, *J* = 1.5, 11.8 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = –4.9 (2 C), 17.7, 24.5, 25.6 (3 C), 28.8 (3 C), 30.0, 37.8, 42.5, 48.7, 65.8, 68.9, 73.1, 73.7, 173.9 ppm. IR (film): $\tilde{\nu}$ = 2953, 2929, 2856, 1730, 1471, 1369, 1250, 1190, 1053, 998, 836 cm^{-1}. ESIMS (MeOH): *m*/*z* (%) = 379.2 (100) $[M + Na]^+$. HRESIMS: calcd. for $C_{19}H_{36}O_4NaSi$ 379.2281; found 379.2270. $C_{19}H_{36}O_4Si \cdot 0.5H_2O$ (356.23): calcd. C 62.42, H 10.20; found C 62.28, H 9.78.

2-*tert*-Butoxy-5-(*tert*-butyldimethylsilanoxy)-1-methyl-cyclohexane-1,4-dicarboxylic Acid (33): Starting from acyloin **12** (200 mg, 0.56 mmol) and using the general procedure, acid–aldehyde **32** (29%, 60.5 mg) and diacid **33** (50%, 108 mg) were obtained after stirring at room temp. for 1.5 h (silica gel chromatography, heptane/EtOAc, 3:1). Both structures were methylated with diazomethane for confirmation. Data for **33**: $[\alpha]_D^{20}$ = +32 (*c* = 1.3, $CHCl_3$). M.p. 144–145 °C (CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.00 (s, 3 H), 0.14 (s, 3 H), 0.84 (s, 9 H), 1.24 (s, 3 H), 1.30 (s, 9 H), 1.37 (m, 1 H), 1.96 (dt, *J* = 3.3, 13.4 Hz, 1 H), 2.34 (q, *J* = 12.0 Hz, 1 H), 2.49 (dt, *J* = 2.7, 12.0 Hz, 1 H), 2.71 (dd, *J* = 3.8, 14.4 Hz, 1 H), 3.50 (dd, *J* = 3.7, 10.9 Hz, 1 H), 4.32 (br. s, 1 H), 10.5 (b, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = –5.6, –4.3, 17.8, 25.9 (3 C), 27.0, 27.8, 28.6 (3 C), 41.8, 45.5, 47.5, 66.6, 75.1, 76.9, 176.0, 177.6 ppm. IR (film): $\tilde{\nu}$ = 3100, 2975, 2931, 2858, 1750, 1711, 1413, 1062, 1001 cm^{-1}. ESIMS (MeOH): *m*/*z* (%) = 411.2 (100) $[M + Na]^+$. HRESIMS: calcd. for $C_{19}H_{36}O_6SiNa$ 411.2179; found 411.2193. $C_{19}H_{36}O_6Si$ (388.23): calcd. C 58.73, H 9.34; found C 58.79, H 9.36.

Esterification of the Free Carboxyl Functionalities with Diazomethane

Dimethyl 2-*tert*-Butoxy-5-(*tert*-butyldimethylsilanoxy)-1-methyl-cyclohexene-1,4-dicarboxylate (34): $TMSCHN_2$ (2 M in ether, 0.3 mL, excess) was added at 0 °C to a solution of diacid **33** (29.7 mg, 0.08 mmol) in a mixture of ether (3 mL) and methanol (0.3 mL). After 15 min, the reaction mixture was evaporated and chromatographed (heptane/EtOAc, 20:1 to 10:1) to afford bis(dimethyl ester) **34** (28.2 mg, 88%): $[\alpha]_D^{20}$ = +36 (*c* = 1.4, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.00 (2 s, 6 H), 0.82 (s, 9 H), 1.17 (s, 9 H), 1.22 (s, 3 H), 1.44 (dd, *J* = 3.1, 14.3 Hz, 1 H), 1.87 (dt, *J* = 3.6, 13.7 Hz, 1 H), 2.47 (dt, *J* = 3.6, 11.0 Hz, 1 H), 2.51 (dd, *J* = 5.0, 14.3 Hz, 1 H), 2.71 (dt, *J* = 10.1, 10.9, 13.7 Hz, 1 H), 3.23 (dd, *J* = 3.3, 10.0 Hz, 1 H), 3.65 (s, 3 H), 3.66 (s, 3 H), 4.22 (dt, *J* = 3.1, 5.0 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.7, –4.1, 18.0, 25.8 (3 C), 26.0, 28.1, 28.8 (3 C), 42.3, 45.8, 47.7, 51.2, 51.3, 67.4, 73.6, 74.9, 172.8, 174.8 ppm. IR (film): $\tilde{\nu}$ = 2953, 2930, 2857, 1747, 1464, 836 cm^{-1}. ESIMS (MeOH): 439.2 (100) $[M + Na]^+$. HRESIMS: calcd. for $C_{21}H_{40}O_6SiNa$ 439.2492; found 439.2513. $C_{21}H_{40}O_6Si \cdot 0.25C_7H_{16}$ (416.26): calcd. C 61.87, H 10.04; found C 61.91, H 10.16.

6-*tert*-Butoxy-8-(*tert*-butyldimethylsilanyloxy)-5-methyl-4-(trimethylsilanyloxy)-3-oxabicyclo[2.2.2]nonan-2-one (35): Starting from bis(silyl)-protected ketone **13** (22 mg, 0.05 mmol) and using the general procedure, lactone **35** (10 mg, 45%) and a mixture of acid–aldehyde **32** and diacid **33** (7.2 mg, 38%, 1:2) were obtained after stirring at room temp. for 22 h (silica gel chromatography, heptane/EtOAc, 3:1). Data for **35**: $[\alpha]_D^{20}$ = +90 (*c* = 0.5, $CHCl_3$). M.p. 81 °C (diethyl ether). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.06 (s, 6 H), 0.19 (s, 9 H), 0.89 (s, 9 H), 0.96 (s, 3 H), 1.15 (s, 9 H), 1.52 (dd, *J* = 9.0, 15.0 Hz, 1 H), 1.85 (dt, *J* = 2.9, 15.3 Hz, 1 H), 2.00 (ddd, *J* = 5.2, 9.0, 15.3 Hz, 1 H), 2.18 (dd, *J* = 3.5, 15.0 Hz, 1 H), 2.98 (td, *J* = 2.3, 5.5 Hz, 1 H), 3.48 (dd, *J* = 3.9, 9.0 Hz, 1 H), 3.90 (ddd, *J* = 3.5, 5.9, 9.0 Hz, 1 H), 5.48 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = –4.9 (2 C), 0.02 (3 C), 18.0, 25.7 (3 C), 28.7 (3 C), 32.8, 36.5, 43.8, 49.2, 66.5, 70.2, 73.6, 99.1, 172.7 ppm. IR (film): $\tilde{\nu}$ = 2958, 2930, 2858, 1734, 1252, 1136, 842 cm^{-1}. ESIMS (MeOH): *m*/*z* (%) = 467.2 (100) $[M + Na]^+$. HRESIMS: calcd. for $C_{22}H_{44}O_5Si_2Na$ 467.2625; found 467.2619. $C_{22}H_{44}O_5Si_2$ (444.27): calcd. C 59.41, H 9.97; found C 59.52, H 9.95.

6-*tert*-Butoxy-4,8-dihydroxy-5-methyl-3-oxabicyclo[3.2.2]nonan-2-one 36 and 5-*tert*-Butoxy-4-formyl-2-hydroxy-4-methylcyclohexanecarboxylic Acid (37): Starting from **14** (21 mg, 0.09 mmol) and using the general procedure, **36** and **37** were obtained (and characterized as a mixture), after stirring at room temp. for 3.5 h in 78% (12.4 mg) combined yield and 4:1 ratio (silica gel chromatography, heptane/EtOAc, 5:1 to EtOAc]. Data for the mixture of **36**/**37**: ^1H NMR (300 MHz, $CDCl_3$): δ = 1.10 (s, 3 H), 1.19 (s, 9 H), 1.74 (m, 1 H), 2.08–2.26 (m, 2 H), 2.35–2.41 (m, 2 H), 3.38 (dd, *J* = 6.3, 10.2 Hz, 1 H), 4.72 (d, *J* = 6.3 Hz, 1 H), 5.32 (s, 1 H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 17.8, 29.0 (3 C), 31.3, 39.4, 46.3, 48.0, 72.4, 73.5, 75.9, 99.2, 177.4 ppm. IR (film): $\tilde{\nu}$ = 3442, 2975, 1714, 1192, 1069 cm^{-1}. ESIMS (MeOH): *m*/*z* = 281.1 (100) $[36 + Na]^+$, 297.1 (32) $[37 + Na]^+$.

8-*tert*-Butoxy-6-hydroxy-1-methyl-4-oxo-3-oxabicyclo[3.2.2]non-2-yl Acetate (38): Baeyer–Villiger oxidation was carried out on bicyclic aldol **16** (30 mg, 0.10 mmol) in dichloromethane (1 mL) for 15 h using the general procedure to give after chromatography (SiO_2,

heptane/EtOAc, 1:1) the corresponding lactone **38** (26 mg, 87%). No bridgehead migration was detected. $[\alpha]_D^{20}$ = +13 (*c* = 1.0, $CHCl_3$). M.p. 131 °C (heptane). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.06 (s, 3 H), 1.14 (s, 9 H), 1.80 (dd, *J* = 6.7, 14.6 Hz, 1 H), 2.01 (dd, *J* = 9.1, 14.6 Hz, 1 H), 2.07 (s, 3 H), 2.12 (dd, *J* = 8.4, 14.8 Hz, 1 H), 2.25 (dt, *J* = 8.3, 14.8 Hz, 1 H), 2.39 (br. s, 1 H), 3.13 (dd, *J* = 4.4, 8.4 Hz, 1 H), 3.45 (t, *J* = 8.4 Hz, 1 H), 4.18 (m, 1 H), 6.17 (s, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.8, 24.5, 28.7 (3 C), 31.0, 39.9, 43.6, 49.2, 64.9, 69.8, 73.3, 98.0, 168.9, 172.9 ppm. IR (film): $\tilde{\nu}$ = 3432, 2972, 1751, 1449, 1364, 1227, 1174, 1100, 1012, 995 cm^{-1}. ESIMS (MeOH): *m*/*z* (%) = 323.1 (100) $[M + Na]^+$. HRESIMS: calcd. for $C_{15}H_{24}O_6Na$ 323.1471; found 323.1448. $C_{15}H_{24}O_6$ (300.15): calcd. C 59.98, H 8.05; found C 59.31, H 8.24.

6-*tert*-Butoxy-8-hydroxy-1,5-dimethyl-3-oxo-2-oxabicyclo[3.3.1]non-9-yl Acetate (41) and 9-*tert*-Butoxy-7-hydroxy-5,7-dimethyl-2-oxo-3-oxabicyclo[3.2.2]non-6-yl Acetate (42): Baeyer–Villiger oxidation was carried out on bicyclic aldol **40** (1.0 g, 3.35 mmol) in CH_2Cl_2 (1 mL) for 20 h by using the general procedure to give after chromatography (SiO_2, CH_2Cl_2/acetone, 4:1) isomeric lactones **41** (572 mg) and **42** (130 mg) in 67% combined yield and 4.4:1 ratio along with recovered **40** (300 mg). Data for **41**: $[\alpha]_D^{20}$ = +75 (*c* = 0.84, $CHCl_3$). M.p. 196–197 °C (heptane). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.90 (s, 3 H), 1.15 (s, 9 H), 1.34 (s, 3 H), 2.10 (s, 3 H), 2.06–2.18 (m, 3 H), 2.20 and 2.48 (ABquartet, *J* = 18.9 Hz, 2 H), 3.40 (t, *J* = 3.0 Hz, 1 H), 3.81 (dd, *J* = 4.8, 11.6 Hz, 1 H), 5.14 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.0, 20.6, 22.3, 28.6 (3 C), 34.7, 37.6, 39.3, 70.5 (2 C), 72.8, 74.7, 85.6, 169.9, 170.5 ppm. ESIMS (MeOH): *m*/*z* (%) = 337.2 (100) $[M + Na]^+$. IR (film): $\tilde{\nu}$ = 3462, 3019, 2972, 2941, 2874, 1723, 1461, 1372, 1270, 1238, 1215, 1064, 1027, 986 cm^{-1}. HRESIMS: calcd. for $C_{16}H_{26}O_6Na$ 337.1627; found 337.1616. $C_{16}H_{26}O_6$ (314.17): calcd. C 61.13, H 8.34; found C 60.56, H 8.23. Data for **42**: $[\alpha]_D^{20}$ = +115 (*c* = 1.1, $CHCl_3$). M.p. 166–167 °C (CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.75 (s, 3 H), 1.15 (s, 9 H), 1.33 (s, 3 H), 1.67 (ddd, *J* = 4.0, 6.5, 15.1 Hz, 1 H), 2.37 (s, 3 H), 2.41 (ddd, *J* = 3.5, 8.8, 15.1 Hz, 1 H), 3.99 (t, *J* = 3.5 Hz, 1 H), 3.68 (dd, *J* = 1.5, 12.2 Hz, 1 H), 3.81 (dd, *J* = 6.5, 8.8 Hz, 1 H), 4.52 (d, *J* = 12.2 Hz, 1 H), 5.03 (d, *J* = 1.5 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.7, 19.9, 27.05, 27.8 (3 C), 31.4, 41.3, 52.4, 67.6, 70.5, 70.8, 73.3, 73.4, 169.2, 172.3 ppm. IR (film): $\tilde{\nu}$ = 3469, 2970, 2939, 2878, 1747, 1715, 1469, 1374, 1364, 1270, 1229, 1178, 1158, 1095, 1058, 998, 913, 752 cm^{-1}. ESIMS (MeOH): *m*/*z* (%) = 337.1 (100) $[M + Na]^+$. HRESIMS calcd. for $C_{16}H_{26}O_6Na$ 337.1627; found 337.1604. $C_{16}H_{26}O_6$ (314.17): calcd. C 61.13, H 8.34; found C 60.62, H 8.06.

Lactone 9: Baeyer–Villiger oxidation was carried out on **20** (70 mg, 0.31 mmol) in $CHCl_2$ (1 mL) for 3 d by using the general procedure to give after chromatography (SiO_2, heptane/EtOAc, 5:1 to EtOAc) **9** in 88% (65 mg) yield along with recovered starting material **20** (5.8 mg, 8%). Data for **9**: $[\alpha]_D^{20}$ = –70 (*c* = 1.1, $CHCl_3$). M.p. 185–186 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.49 (s, 3 H), 1.53 (s, 3 H), 1.57 (s, 3 H), 2.27 (ddd, *J* = 1.1, 5.9, 16.6 Hz 1 H), 2.39–2.48 (m, 3 H), 2.99 (dd, *J* = 7.1, 19.2 Hz, 1 H), 3.87 (d, *J* = 1.2 Hz, 1 H), 4.28 (t, *J* = 1.2 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.1, 21.6, 27.5, 34.0, 36.8, 39.0, 72.0, 79.3, 79.9, 83.5, 119.5, 170.0 ppm. IR (film): $\tilde{\nu}$ = 3423, 1712, 1409, 1300, 1264, 1197, 1176, 1111, 1037, 858 cm^{-1}. ESIMS (MeOH): *m*/*z* (%) = 263.1 (100) $[M + Na]^+$. HRESIMS (CH_2Cl_2): calcd. for $C_{12}H_{16}O_5Na$ 263.0891; found: 263.0895.

Supporting Information (see also the footnote on the first page of this article): Experimental procedures for the synthesis and spectral characterization of all compounds investigated, including those presented here, and X-ray crystallographic data for **43**.

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[14] The cation-stabilizing effect of the unshared oxygen electrons increased the relative migratory aptitude of the attached carbon.

[15] Following hydrolytic opening and dehydration (Burgess), 41 should lead to a taxoid C-ring precursor containing an exocyclic C4,20 olefin − a useful taxoid right-half building block.

[16] An α-bromine atom usually retards migration of the attached carbon.

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