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Stereoselective α,α′-Annelation Reactions of 1,3-Dioxan-5-ones

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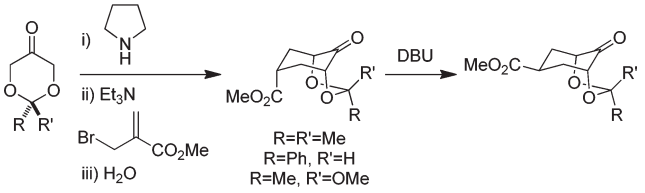
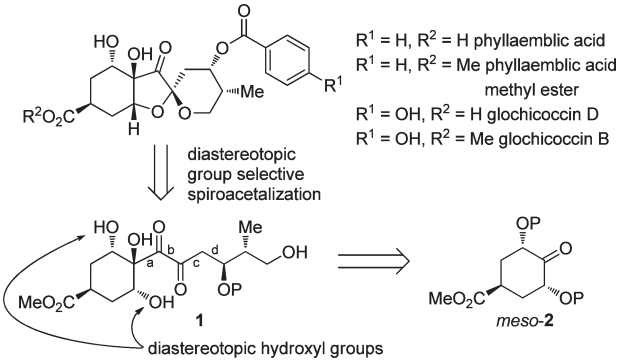


Pyrrolidine enamines derived from three 1,3-dioxan-5-ones undergo α,α′-annelation reactions with methyl α-(bromomethyl)acrylate to produce bridged 2,4-dioxabicyclo[3.3.1]-nonane ring systems with complete stereocontrol. Stereochemical outcomes have been rationalized based on steric and stereoelectronic interactions in intermediate boat-like conformations of the 1,3-dioxane ring and subsequent kinetic protonation to set an axial ester group on the cyclohexanone ring. Base-mediated ester epimerization provides the stereochemical array found in the highly oxygenated cyclohexane ring of phyllaemblic acid and glochicoccins B and D.

Phyllaemblic acid is a highly oxygenated, norbisabolane sesquiterpene isolated, along with its methyl ester and three ester glycosides, phyllaemblicins A−C, from the roots of *Phyllanthus emblica* L., a plant widely distributed in subtropical and tropical areas of China, India, Indonesia, and the Malay Peninsula.[1,2] The rhizomes of a related genus *Glochiddion coccineum*, also widely distributed in China, were found to contain the structurally similar glochicoccins B and D (Scheme 1).[3] Both these plants have long been used in traditional folk medicine by the indigenous people of these regions for the treatment of a range of ailments.

SCHEME 1. Retrosynthetic Analysis



Despite their potential biological activity, approaches toward the syntheses of these natural products have yet to be reported. Although structurally related to the extensively investigated phyllanthocins,[4] the presence of an additional alcohol functionality in the cyclohexane ring suggests a unique strategy can be adopted based on the presence of a latent symmetry element, revealed upon disconnection of the spiroacetal (Scheme 1). This functionality could conceivably arise through a plausible biomimetic spiroacetalization reaction, engaging one of the two diastereotopic hydroxyl groups on the cyclohexane ring of **1**.[5] The latent symmetry element can be exploited synthetically by further disconnection of **1** along any of the bonds a−d to two fragments of approximately equal complexity, only one of which need be chiral. We have targeted *meso*-2,4,6-trisubstituted cyclohexanone **2** as a suitable building block to investigate such an approach, and in this Note we report a concise, stereoselective synthesis of this system based on an α,α′-annelation reaction of 1,3-dioxan-5-ones.

The α,α′-annelation of enamines with *bis*electrophiles such as ethyl α-(bromomethyl)acrylate has been applied to the synthesis of a range of cyclic ketones with diverse application in organic chemistry.[6−8] The transformation shown in Scheme 2 is typical: a bridged bicyclic ring system is formed as a single stereoisomer, with the axial ester stereochemistry arising through in situ kinetic protonation from the less-hindered face, either of an ester enolate or in concert with C−C bond formation. Application of this methodology in the synthesis of **2** was envisaged

(1) Zhang, Y.-J.; Tanaka, T.; Iwamoto, Y.; Yang, C.-R.; Kouno, I. *Tetrahedron Lett*. **2000**, *41*, 1781.
(2) (a) Zhang, Y.-J.; Tanaka, T.; Iwamoto, Y.; Yang, C.-R.; Kouno, I. *J. Nat. Prod*. **2000**, *63*, 1507. See also: (b) Zhang, Y.-J.; Tanaka, T.; Iwamoto, Y.; Yang, C.-R.; Kouno, I. *J. Nat. Prod*. **2001**, *64*, 870.
(3) Xiao, H.-T.; Hao, X.-Y.; Yang, X.-W.; Wang, Y.-H.; Lu, Y.; Zhang, Y.; Gao, S.; He, H.-P.; Hao, X.-J. *Helv. Chim. Acta* **2007**, *90*, 164.
(4) For a review of synthetic approaches toward phyllanthocin and breynolide see: Smith, A. B.; Empfield, J. R. *Chem. Pharm. Bull*. **1999**, *47*, 1671.
(5) For reviews on diastereotopic group selective reactions see: (a) Studer, A.; Schleth, F. *Synlett* **2005**, 3033. (b) Hoffmann, R. W. *Synthesis* **2004**, 2075.
(6) (a) Nelson, R. P.; Lawton, R. G. *J. Am. Chem. Soc*. **1966**, *88*, 3884. (b) Nelson, R. P.; McEuan, J. M.; Lawton, R. G. *J. Org. Chem*. **1969**, *34*, 1225. (c) McEuan, J. M.; Nelson, R. P.; Lawton, R. G. *J. Org. Chem*. **1970**, *35*, 690. (d) Lawton, R. G.; Dunham, D. J. *J. Am. Chem. Soc*. **1971**, *93*, 2074. (e) Haslander, M.; Zawacky, S.; Lawton, R. G. *J. Org. Chem*. **1976**, *41*, 1807. (f) Weiss, D. S.; Haslanger, M.; Lawton, R. G. *J. Am. Chem. Soc*. **1976**, *98*, 1050. (g) Chen, Y.-S.; Kampf, J. W.; Lawton, R. G. *Tetrahedron Lett*. **1997**, *38*, 5781.
(7) (a) Stetter, H.; Thomas, H. G. *Angew. Chem., Int. Ed*. **1967**, *6*, 554. (b) Stetter, H.; Thomas, H. G. *Chem. Ber*. **1968**, *101*, 1115. (c) Stetter, H.; Thomas, H. G.; Meyer, K. *Chem. Ber*. **1970**, *103*, 863. (d) Stetter, H.; Komorowski, K. *Chem. Ber*. **1971**, *104*, 75. (e) Stetter, H.; Elfert, K. *Synthesis* **1974**, 36. (f) Stetter, H.; Rämsch, K.-D.; Elfert, K. *Liebigs. Ann. Chem*. **1974**, 1322.

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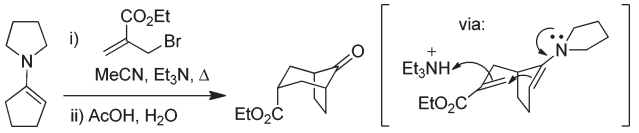
SCHEME 2. Lawton's α,α′-Annelation Reaction[6b]



through employment of a suitably protected dihydroxyacetone derived enamine, with the use of a cyclic acetal protecting group removing any ambiguity in enamine geometry[9] and hence ensuring both oxygen substituents reside on the same side of the resulting cyclohexanone ring.

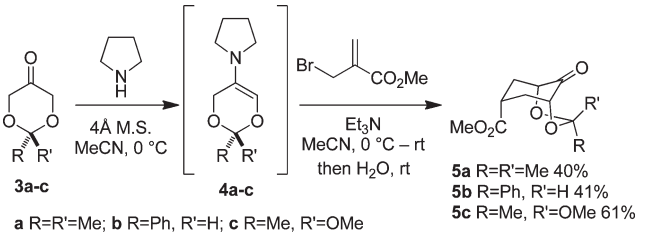
Our studies began with the known acetonide **3a**, prepared in three steps from commercially available material.[10] The enamine **4a** was formed under standard conditions, and could be purified by distillation, albeit in a modest 53% yield, reflecting its thermal instability. Subjecting **4a** to standard α,α-annelation reaction conditions with methyl α-(bromomethyl)acrylate (refluxing MeCN followed by iminium hydrolysis with aqueous acetic acid) gave the desired bicyclic ketone **5a** in 19% yield.

To increase the yield of **5a** a series of modifications to the standard conditions were undertaken. Isolation of the enamine was avoided, and the reaction mixture was directly subjected to the α,α′-annelation reaction. This reaction in turn was found to be higher yielding at lower temperatures. The iminium hydrolysis was affected by simple addition of water, which avoided potential cleavage of the acetal under overly acidic conditions. In this manner, the yield of **5a** could be increased to 40% over two steps (Scheme 3).

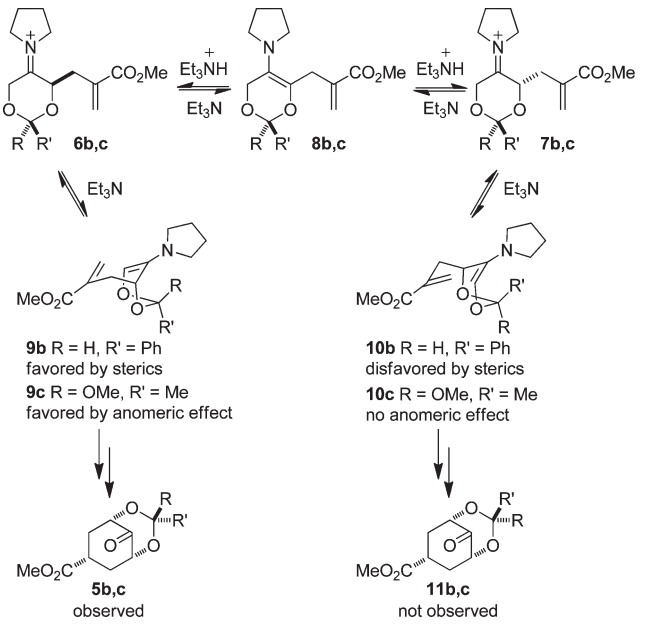
The structure of **5a** was deduced by NMR spectroscopy and X-ray crystallography (see the Supporting Information).[11] A "chair-boat" conformation is adopted in both the solid state and in solution, with no evidence of ring-flipping from variable-temperature NMR experiments.[12] The ester group is axially oriented on the cyclohexanone ring, cis to the two oxygen substituents.

The optimized reaction conditions were applied to the more readily synthesized 1,3-dioxan-5-ones **3b** and **3c**.[10,13]

SCHEME 3. α,α′-Annelation of 1,3-Dioxan-5-ones



SCHEME 4. Stereochemical Rationale



A comparable 41% yield was obtained for the benzylidene acetal **5b**, whereas the ortho acetal **5c** was prepared in an improved 61% yield. In both cases a single stereoisomer was formed. The relative stereochemistry in **5b** was determined by NOE analysis and X-ray crystallography.[11] A chair-boat conformation is again adopted, with the phenyl substituent residing pseudoequatorial on the dioxanone ring. The relative stereochemistry in **5c** was tentatively assigned by NOE analysis, and confirmed by X-ray analysis of **12c** after ester epimerization (vide infra).[11]

The stereochemical outcome in the α,α′-annelation reaction of enamines **4b** and **4c** can be rationalized by considering the reaction mechanism shown in Scheme 4. *C*-Allylation of enamine **4b**,**c** gives rise to two possible iminiums, **6b**,**c** and **7b**,**c** (identical starting from **4a**). These are in equilibrium with enamines **9b**,**c** and **10b**,**c** under the reaction conditions. For the subsequent C−C bond formation, enamines **9b**,**c** and **10b**,**c** must adopt boat conformations to orient the allylic ester axial.[14] This conformation is disfavored for **10b** by a steric interaction of the flagpole Ph group with the pyrrolidine ring, hence **9b** is favored and **5b** is the observed product. The corresponding steric interactions for **9c** and **10c** are less pronounced, but here the additional anomeric stabilizing

(8) (a) Speckamp, W. N.; Dijkink, J.; Huisman, H. O. *J. Chem. Soc. D* **1970**, 196. (b) Speckamp, W. N.; Dijkink, J.; Huisman, H. O. *J. Chem. Soc. D* **1970**, 197. (c) Speckamp, W. N.; Dijkink, J.; Dekkers, W. J. D.; Huisman, H. O. *Tetrahedron* **1971**, *27*, 3143. (d) Peters, J. A.; Van Der. Toorn, J. M.; Van Bekkum, H. *Tetrahedron* **1974**, *30*, 633. (e) Gompper, R.; Ulrich, W.-R. *Angew. Chem., Int. Ed.* **1976**, *15*, 299. (f) Peters, J. A.; Van De Graff, B.; Schuyl, P. J. W.; Wortel, Th. M.; Van Bekkum, H. *Tetrahedron* **1976**, *32*, 2735. (g) Momose, T.; Muraoka, O. *Chem. Pharm. Bull.* **1978**, *26*, 2217. (h) Bok, Th. B.; Speckamp, W. N. *Tetrahedron* **1979**, *35*, 267. (i) Meeuwissen, H. J.; Van Der Knaap, T. A.; Bickelhaupt, F. *Tetrahedron* **1983**, *39*, 4225. (j) Anzeveno, P. B.; Matthews, D. P.; Barney, C. L.; Barbuch, R. J. *J. Org. Chem.* **1984**, *49*, 3134. (k) Seebach, D.; Missbach, M.; Calderari, G.; Eberle, M. *J. Am. Chem. Soc.* **1990**, *112*, 7625. (l) Padwa, A.; Kline, D. N.; Murphree, S. S.; Yeske, P. E. *J. Org. Chem.* **1992**, *57*, 298. (m) Nemes, P.; Janke, F.; Scheiber, P. *Liebigs Ann. Chem.* **1993**, 179. (n) Ayres, F. D.; Khan, S. I.; Chapman, O. L.; Kaganove, S. N. *Tetrahedron Lett.* **1994**, *35*, 7151. (o) Yeh, V. S. C.; Kurukulasuriya, R.; Madar, D.; Patel, J. R.; Fung, S.; Monzon, K.; Chiou, W.; Wang, J.; Jacobson, P.; Sham, H. L.; Link, J. T. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5408. (p) Cao, C.-L.; Zhou, Y.-Y.; Zhou, J.; Sun, X.-L.; Tang, Y.; Li, Y.-X.; Li, G.-Y.; Sun, J. *Chem.—Eur. J.* **2009**, *15*, 11384.

(9) For a review on the synthetic utility of dihydroxyacetone derivatives see: Enders, D.; Voith, M.; Lenzen, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 2.

(10) Forbes, D. C.; Ene, D. G.; Doyle, M. P. *Synthesis* **1988**, 879.

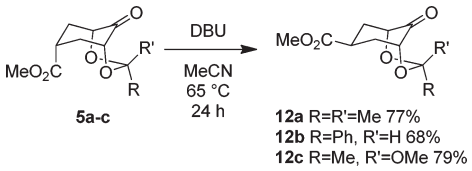
(11) A file in CIF format is available in the Supporting Information. CCDC 779722 - 779726 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/datarequest/cif.

(12) For a review on conformational analysis of bicyclo[3.3.1]nonanes and their heteroanalogues see: Zefirov, N. S.; Palyulin, V. A. *Top. Stereochem.* **1991**, *20*, 171.

(13) Peukert, S.; Giese, B. *J. Org. Chem.* **1998**, *63*, 9045.

(14) Peters has proposed that α,α′-annelation reactions can proceed through an alternative half-chair transition state (ref 8d). Application of this model to **9b**,**c** and **10b**,**c** fails to predict the observed isomer.

SCHEME 5. Base-Mediated Ester Epimerization



interaction is only present for **9c**, ultimately favoring formation of **5c**.

In all cases the axial ester group is consistent with an in situ kinetic protonation, as is typically observed in other α, α′-annelation reactions.[6−8]

Ester epimerization of **5a**−**c** was best achieved by using DBU in acetonitrile at 65 °C (Scheme 5). Upon epimerization, there is a diagnostic downfield shift of the proton adjacent to the ester group, presumably due to its alignment with the two axial oxygen substituents on the cyclohexanone ring,[15] suggesting the overall chair-boat conformation is maintained. This is consistent with NOE and variable-temperature NMR studies, and X-ray crystal structure analysis, of **12a**−**c**.[11] The resulting stereochemical array in **12a**−**c** corresponds to that of target compound *meso*-**2**.

In summary, the α,α′-annelation reaction of 1,3-dioxan-5-ones provides a convenient method for the synthesis of usefully substituted *meso*-cyclohexanones **5** and **12**, embedded within a 2,4-dioxabicyclo[3.3.1]nonane ring system. Use of these building blocks in target synthesis is currently under investigation.

Experimental Section

α,α′-Annelation of 1,3-Dioxan-5-ones (Procedure A): Methyl 3,3-Dimethyl-9-oxo-2,4-dioxabicyclo[3.3.1]nonane-7α-carboxylate (5a) To an ice-cooled solution of 2,2-dimethyl-1,3-dioxan-5-one[10] (**3a**) (0.501 g, 3.85 mmol) in anhydrous acetonitrile (10 mL) was added molecular sieves (4 Å, 4.00 g) and pyrrolidine (0.274 g, 3.85 mmol). The solution was stirred at 0 °C (external ice-bath temperature) for 5 h under an inert atmosphere. Triethylamine (0.39 g, 3.86 mmol) was added, followed by a solution of methyl α-(bromomethyl)acrylate[16] (0.69 g, 3.85 mmol) in acetonitrile (30 mL) dropwise under an inert atmosphere. A precipitate quickly formed and redissolved. The resulting yellow solution was stirred for 16 h with gradual warming to room temperature. The solution was filtered to remove the molecular sieves, distilled water (40 mL) was added, and the resulting mixture was stirred at room temperature for 5 h. The mixture was then extracted with dichloromethane (3 × 40 mL), dried over anhydrous Na_2SO_4, and filtered, then the solvents were removed under vacuum. Purification by column chromatography (3:1 hexane:diethyl ether) afforded the title compound as a white solid (0.353 g, 40%): R_f 0.25 (1:1 hexane:diethyl ether); mp 65−67 °C; υ_{max} (nujol mull)/cm^{-1} 1745, 1456, 1023, 992; δ_H (300 MHz, $CDCl_3$) 1.35 (3H, s, CH_3), 1.36 (3H, s, CH_3), 1.99 (2H, dd, J = 7.2, 14.4 Hz, CH_2), 2.58 (1H, t, J = 7.2 Hz, CHCO$_2$CH$_3$), 3.27 (2H, m, CH_2), 3.76 (3H, s, CO$_2$CH_3), 4.28 (2H, d, J = 3.9 Hz, CHCO); δ_c (75.5 MHz, $CDCl_3$) 24.9 (CH_3), 27.9 (CH_3), 33.8 (CH), 38.8 (CH_2), 52.2 (CH_3), 76.8 (CH), 99.2 (C), 173.8 (C), 215.3 (C); m/z (EI) 229.1 [M + H]$^+$. Anal. Calcd for $C_{11}H_{16}O_5$: C, 57.88; H, 7.07. Found C, 57.77; H, 7.00.

Methyl 9-Oxo-3α-phenyl-2,4-dioxabicyclo[3.3.1]nonane-7α-carboxylate (5b). Procedure A was employed with use of 2-phenyl-1,3-dioxan-5-one[10] (**3b**) (1.986 g, 11.2 mmol). Column chromatography (3:1 hexane:diethyl ether) afforded the title compound as a white solid (1.270 g, 41%); R_f 0.26 (1:1 hexane:diethyl ether); mp 101−104 °C; υ_{max} (neat)/cm^{-1} 1747, 1718, 1456, 1016, 989; δ_H (500 MHz, $CDCl_3$) 2.12 (2H, dd, J = 7.6, 15.2 Hz, CH_2), 2.68 (1H, t, J = 7.2 Hz, CHCO$_2$CH$_3$), 3.42−3.50 (2H, m, CH_2), 3.58 (3H, s, CO$_2$CH_3), 4.60 (2H, d, J = 3.9 Hz, CHCO), 5.70 (1H, s, PhCH), 7.35−7.51 (5H, m, Ph-H); δ_c (75.5 MHz, $CDCl_3$) 33.7 (CH), 38.0 (CH_2), 52.1 (CH_3), 80.7 (CH), 98.5 (CH), 126.2 (CH), 128.2 (CH), 129.3 (CH), 136.3 (C), 173.6 (C), 212.9 (C); m/z (ES) 299.1 [M + Na]$^+$, HRMS (ES) [M + Na]$^+$ 299.0901, $C_{15}H_{16}O_5Na$ requires 299.0895.

Methyl 3β-Methoxy-3α-methyl-9-oxo-2,4-dioxabicyclo[3.3.1]nonane-7α-carboxylate (5c). Procedure A was employed with use of 2-methoxy-2-methyl-1,3-dioxan-5-one[13] (**3c**) (1.500 g, 10.3 mmol). Column chromatography (3:1 hexane:diethyl ether) afforded the title compound as a viscous pale yellow oil (1.530 g, 61%); R_f 0.51 (1:1 hexane:diethyl ether); υ_{max} (neat)/cm^{-1} 1731, 1441, 1046, 1010; δ_H (300 MHz, $CDCl_3$) 1.41 (3H, s, CH_3), 1.97 (2H, dd, J = 7.1, 14.2 Hz, CH_2), 2.62 (1H, t, J = 7.0 Hz, CHCO$_2$CH$_3$), 3.19−3.25 (5H, m, OCH_3, CH_2), 3.75 (3H, s, CO$_2$CH_3), 4.16 (2H, d, J = 3.9 Hz, CHCO); δ_c (100 MHz, $CDCl_3$) 19.7 (CH_3), 33.8 (CH), 36.4 (CH_2), 50.9 (CH_3), 51.9 (CH_3), 75.0 (CH), 111.8 (C), 173.5 (C), 207.8 (C); m/z (ES) 267.1 [M + Na]$^+$, HRMS (ES) [M + Na]$^+$ 267.0842, $C_{11}H_{16}O_6Na$ requires 267.0845.

Ester Epimerization:. Methyl 3,3-Dimethyl-9-oxo-2,4-dioxabicyclo[3.3.1]nonane-7β-carboxylate (12a) Methyl 3,3-dimethyl-9-oxo-2,4-dioxabicyclo[3.3.1]nonane-7α-carboxylate (**5a**) (0.053 g, 0.232 mmol) was dissolved in acetonitrile (3 mL) followed by addition of DBU (0.035 g, 0.230 mmol). The reaction mixture was heated at 65 °C (external temperature) for 24 h, allowed to cool, and concentrated to approximately half volume. Column chromatography (4:1 hexane:diethyl ether) afforded the title compound as a white solid (0.041 g, 77%); R_f 0.47 (1:1 hexane:diethyl ether); mp 79−82 °C; υ_{max} (nujol mull)/cm^{-1} 1754, 1455, 1006, 964; δ_H (400 MHz, $CDCl_3$) 1.42 (3H, s, CH_3), 1.50 (3H, s, CH_3), 1.93 (2H, t, J = 13.4 Hz, CH_2), 2.60 (2H, m, CH_2), 3.55 (1H, tt, J = 4.6, 12.6 Hz, CHCO$_2$CH$_3$), 3.67 (3H, s, CO$_2$CH_3), 4.28 (2H, d, J = 3.8 Hz, CHCO); δ_c (75.5 MHz, $CDCl_3$) 25.0 (CH_3), 28.5 (CH_3), 33.0 (CH), 40.3 (CH_2), 52.0 (CH_3), 76.0 (CH), 98.7 (C), 174.2 (C), 214.0 (C); m/z (ES) 251.1 [M + Na]$^+$, HRMS (ES) [M + Na]$^+$ 251.0891, $C_{11}H_{16}O_5Na$ requires 251.0895.

Methyl 9-Oxo-3α-phenyl-2,4-dioxabicyclo[3.3.1]nonane-7β-carboxylate (12b). Methyl 9-oxo-3α-phenyl-2,4-dioxabicyclo-[3.3.1]nonane-7α-carboxylate (**5b**) (0.062 g, 0.526 mmol) was dissolved in acetonitrile (3 mL) followed by addition of DBU (0.034 g, 0.526 mmol). The reaction mixture was heated at 65 °C (external temperature) for 24 h, allowed to cool, and concentrated to approximately half volume. Column chromatography (4:1 hexane:diethyl ether) afforded the title compound as a white solid (0.042 g, 68%); R_f 0.38 (1:1 hexane:diethyl ether); mp 113−116 °C; υ_{max} (neat)/cm^{-1} 1750, 1722, 1453, 1103, 1071; δ_H (300 MHz, $CDCl_3$) 2.08 (2H, t, J = 13.7 Hz, CH_2), 2.70−2.85 (2H, m, CH_2), 3.70 (3H, s, CO$_2$CH_3), 3.73 (1H, tt, J = 4.6, 12.5 Hz, CHCO$_2$CH$_3$), 4.59 (2H, d, J = 3.8 Hz, CHCO), 5.76 (1H, s, PhCH), 7.40−7.60 (5H, m, Ph-H); δ_c (75.5 MHz, $CDCl_3$) 33.1 (CH), 39.6 (CH_2), 52.1 (CH_3), 79.8 (CH), 98.0 (CH), 126.1 (CH), 128.4 (CH), 129.6 (CH), 136.4 (C), 174.1 (C), 211.7 (C); m/z (ES) [M + Na]$^+$ 299.1, HRMS (ES) [M + Na]$^+$ 299.0898, $C_{15}H_{16}O_5Na$ requires 299.0895.

Methyl 3β-Methoxy-3α-methyl-9-oxo-2,4-dioxabicyclo[3.3.1]nonane-7β-carboxylate (12c). Methyl 3β-methoxy-3α-methyl-9-oxo-2,4-dioxabicyclo[3.3.1]nonane-7α-carboxylate (**5c**) (1.300 g, 5.328 mmol) was dissolved in acetonitrile (50 mL) followed by

(15) Pretsch, E.; Bühlmann, P.; Badertscher, M. *Structure Determination of Organic Compounds*, 4th ed.; Springer-Verlag: Berlin, Germany, 2009; p 176.

(16) Borrell, J. I.; Teixidó, J.; Martínez-Teipel, B.; Matallana, J. L.; Copete, M. T.; Llimargas, A.; García, E. *J. Med. Chem.* **1998**, *41*, 3539.

addition of DBU (0.810 g, 5.329 mmol). The reaction mixture was heated at 65 °C (external temperature) for 24 h, allowed to cool, and concentrated to approximately half volume. Column chromatography (4:1 hexane:diethyl ether) afforded the title compound as a white solid (1.030 g, 79%); R_f 0.68 (1:1 hexane:diethyl ether); mp 34−36 °C; υ_{max} (neat)/cm^{-1} 1754, 1731, 1434, 1047, 918; δ_H (300 MHz, $CDCl_3$) 1.59 (3H, s, CH_3), 1.96 (2H, t, J = 13.6 Hz, CH_2), 2.62 (2H, m, CH_2), 3.27 (3H, s, OCH_3), 3.46 (1H, tt, J = 4.5, 12.5 Hz, CHCO$_2$CH$_3$), 3.71 (3H, s, CO$_2$CH_3), 4.20 (2H, d, J = 3.6 Hz, CHCO); δ_c (100 MHz, $CDCl_3$) 20.2 (CH_3), 33.2 (CH), 38.1 (CH_2), 50.9 (CH_3), 52.0 (CH_3), 74.5 (CH), 112.0 (C), 174.1 (C), 206.8 (C); m/z (ES) 267.1 $[M + Na]^+$, HRMS (ES) $[M + Na]^+$ 267.0850, $C_{11}H_{16}O_6Na$ requires 267.0845.

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Supporting Information Available: Copies of ^{1}H and ^{13}C NMR for all new compounds, including NOE and variable temperature analyses, and X-ray crystal data of **5a**, **5b**, **12a**, **12b**, and **12c** as CIF files. This material is available free of charge via the Internet at http://pubs.acs.org.