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PAPER

A one-pot sequence for the efficient synthesis of highly functionalized macrocarbocycles or bridged 2,8-dioxabicyclo[3.2.1]octanes from 1-nitrobicyclic compounds†

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The reaction of 1-nitrobicyclo[*n*.3.1]alkane-(6 + *n*)ones with sodium borohydride followed by acidic workup led to ring opening *via* a one-pot sequence comprising the retro-Dieckmann-type opening of the α-nitroketone structural fragment, followed by aldehyde reduction and a final Nef reaction, leading to highly functionalized 12 to 14-membered carbocyclic ketones bearing three stereocenters, which are adjacent in some of the compounds. The reactions starting from 1-nitrobicyclo[9.3.1]pentadecan-15-ones could be adjusted to give macrocyclic 2,8-dioxabicyclo[3.2.1]octanes containing an additional bridge by diastereoselective formation of a third ring and a fourth stereocenter through acid-promoted intramolecular ketal formation. This is a very interesting ring system related to the core of the zaragozic acid family of natural products.

Introduction

The synthesis of macroheterocyclic compounds has received much attention, particularly in the field of supramolecular chemistry.[1] In contrast, the preparation of medium-sized carbocycles (8–11 ring size) and, in particular, macrocarbocyclic compounds (12 or higher ring size) is still very challenging with the methods currently available. The most common strategy for the synthesis of these compounds involves the connection of the ends of a linear precursor.[2] In order to avoid polymerization processes, these reactions must normally be carried out under high dilution conditions and their yields are normally moderate. One solution to this problem may consist of the use of a temporary connection to aid the macrocyclization,[3] but this requires additional steps. Alternatively, the use of ring expansion-based strategies often allows one to overcome these problems.[4]

We describe in this paper the diastereoselective preparation of highly functionalized macrocarbocycles by a domino process involving the reductive ring expansion of bicyclic compounds containing an α-nitroketone function with the nitro group in a bridgehead position,[5] coupled with a Nef reaction and, in some cases, with the *in situ* construction of a bridged 2,8-dioxabicyclo [3.2.1]octane system by intramolecular formation of two acetal bonds. By using starting materials containing an α-nitroketone moiety, we expected to take advantage of the high stability of nitronate anions to effect the desired ring opening by nucleophilic attack on the carbonyl group. This is a known strategy for the preparation of carbocycles by ring opening of bicyclic systems. Thus, Rodriguez has developed the so-called MARDi cascade, consisting of the synthesis of functionalized cycloheptene derivatives by preparation of bicyclo[3.2.1]octanes *via* a Michael–aldol domino sequence from 2-oxocyclopentane-1-carboxylate esters and α,β-unsaturated aldehydes in the presence of base, followed by *in situ* opening of the five-membered ring through a retro-Dieckmann reaction.[6] Hesse has described some isolated examples of the opening of bicyclic compounds containing an α-nitroketone function by alkoxide anions, especially in the context of the total synthesis of muscone, although without studying their stereochemistry, which was of no consequence for his purpose. Indeed, the ring-opening reactions were carried out on mixtures of diastereomers.

Results and discussion

We started our study by investigating the stereochemical outcome of the opening of diastereomerically pure compound **1** by a hydroxide anion, and obtained the 14-membered carbocycle **2** in a moderate 35% yield and as a 1 : 1 mixture of two diastereomers at the stereocenter adjacent to the nitro group, together with their *aci* tautomer. This showed that the ring-opening reaction respected all pre-existing stereocenters of the bicyclic compound, but, not unexpectedly, the final protonation of the nitronate anion resulting from ring opening lacked diastereoselectivity (Scheme 1).

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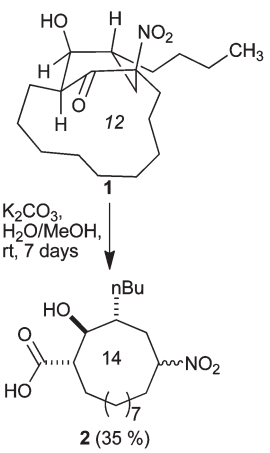
The result summarized in Scheme 1 prompted us to study opening of the six-membered ring of our bicyclic starting materials by other nucleophiles. After some experimentation, we discovered that hydride donors were an acceptable option, and gave the results summarized in Scheme 2 and Table 1. The reaction afforded 12 to 14-membered carbocycles (compounds **3**) and presumably proceeded by a domino mechanism involving opening of the α-nitroketone moiety *via* a retro Dieckmann-type mechanism, facilitated by the high stability of the resulting nitronate anion. This would be followed by an *in situ* reduction of the aldehyde group generated during ring opening and a final protonation of the nitronate anion during workup which, as in the previous case, was not diastereoselective (Scheme 2).

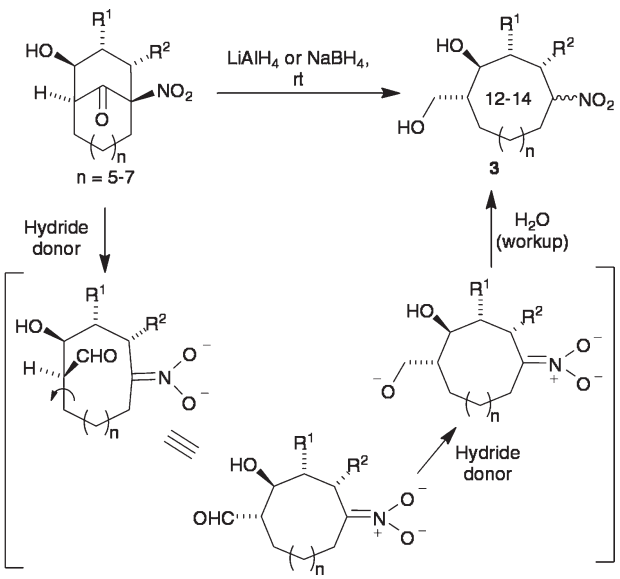
At this stage, we reasoned that it should be possible to combine the ring-opening process with a Nef reaction,[7] potentially leading to a one-pot synthesis of diastereomerically pure macrocarbocycles with a high degree of substitution and functionalization. To this end, we chose the sodium borohydride conditions, which we expected to be more amenable to combination with acidic conditions in a one-pot procedure, for safety reasons. Pleasingly, our expectation was borne out by experience, as shown by the results collected in Scheme 3 and Table 2. Furthermore, although the transformation of nitroalkanes into ketones normally requires strongly acidic conditions, long reaction times and/or high temperatures,[8] in our case we found that it was normally enough to use a moderately acidic workup at room temperature following the reaction with sodium borohydride. For the cases where $n = 5$ or 6, the reaction products were the 12- or 13-membered macrocarbocycles **5a–c** or **5d–f**, respectively, containing three stereocenters (which are adjacent in some of the compounds), and were isolated as single diastereomers. The unusual ease of the Nef reaction contributed to the practical usefulness of our method and can be attributed to assistance from the hydroxy γ to the protonated group (structure **4** in Scheme 3). Interestingly, for the case $n = 7$, compounds **5** were also isolated in some cases (entries 8, 10 and 12) but, due to the presence of two hydroxyl groups and one carbonyl group at a suitable distance, these reactions could be made to undergo a double intramolecular acetalyzation reaction to give hitherto unknown macrocyclic bridged 2,8-dioxabicyclo[3.2.1]octanes **6** as the sole reaction products simply by increasing the time of exposure to the acidic conditions or, in some cases, by increasing the concentration of acid.[9] This one-pot access to derivatives of the 2,8-dioxabicyclo[3.2.1]octane ring system is particularly interesting because of its presence in natural products belonging to the zaragozic acid family (Fig. 1), which have received much synthetic attention,[10] prompted by their challenging structures and their ability to reduce cholesterol blood levels by inhibiting squalene synthase.[11]

Conclusions

In conclusion, we have developed a simple, new method for the generation of highly functionalized macrocarbocyclic ketones in diastereomerically pure form starting from 1-nitrobicyclo[*n*.3.1]alkane-(6 + *n*)ones, based on a one-pot sequence of three reactions, namely opening of a six-membered ring by addition–



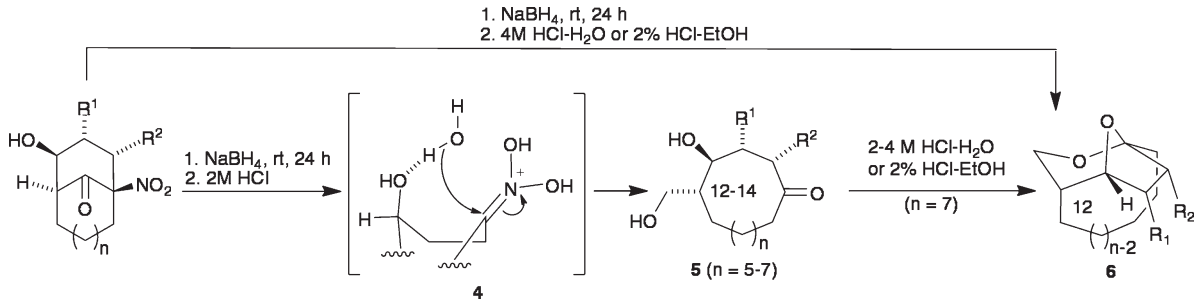
Scheme 1 Investigation of the stereochemical outcome of the opening of a derivative of 1-nitrobicyclo[9.3.1]pentadecan-15-one by a hydroxide anion.



Scheme 2 Domino sequence comprising ring-opening of nitrobicycles by a hydride anion and aldehyde reduction, leading to 12 to 14-membered carbocycles **3**.

Table 1 Results obtained in the opening of nitrobicyclic substrates with hydride donors followed by aqueous workup

Entry	Cmpd	R^1	R^2	*n*	Reagent	Time (h)	Yield (%)	d.r.
1	**3a**	H	Me	5	$LiAlH_4$	4.5	69	4.5 : 1
2	**3b**	*n*Bu	H	6	$NaBH_4$	3	85	1 : 1
3	**3c**	*n*Bu	H	7	$NaBH_4$	3	65	2 : 1
4	**3d**	H	Me	7	$LiAlH_4$	4	37	1.3 : 1

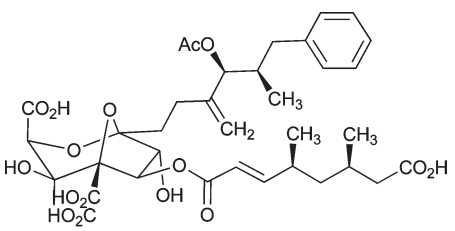


Scheme 3 One-pot transformation of nitrobicycles into macrocarbocyclic ketones **5** or macrocyclic bridged 2,8-dioxabicyclo[3.2.1]octanes **6**.

Table 2 Conditions and yields for the synthesis of macrocyclic compounds **5** and **6**

Entry	Product	R^1	R^2	*n*	Reaction time (Nef for **5**, Nef/ketalization for **6**) (h)	Yield of **5** (%)	Yield of **6** (%)
1	**5a**	H	H	5	1	62	0
2	**5b**	CH_3	H	5	5	80	0
3	**5c**	H	CH_3	5	5	84[a]	0
4	**5d**	H	H	6	12	51	0
5	**5e**	CH_3	H	6	3	64	0
6	**5f**	H	CH_3	6	3	56[a]	0
7	**6g**	H	H	7	1	0	100
8	**5g**	CH_3	H	7	1	100	0
9	**6h**	CH_3	H	7	48	0	94[b]
10	**5i**/**6i**	*n*-C_4H_9	H	7	2	45	45
11	**6i**	*n*-C_4H_9	H	7	48	0	90[b]
12	**5j**/**6j**	H	CH_3	7	2	49	49
13	**6j**	H	CH_3	7	48	0	99[a,b]

[a] The stereocenter adjacent to the carbonyl was epimerized to give 1 : 1 (for **5c** and **6j**) and 2 : 1 (for **5f**) mixtures. [b] 4 M HCl was used.



Zaragozic acid A (squalestatin 1)

Fig. 1 Structure of a representative of the zaragozic acid family, natural derivatives of the 2,8-dioxabicyclo[3.2.1]octane system.

elimination of a hydride to an α-nitroketone structural unit, reduction of an aldehyde group and a Nef reaction. Furthermore, in the reactions starting from 1-nitrobicyclo[9.3.1]pentadecan-15-ones, the length of the domino sequence could be increased by two steps (formation of a cyclic ketal) by increasing the acidity of the workup conditions, leading to a one-pot synthesis of novel macrocyclic bridged derivatives of the 2,8-dioxabicyclo-[3.2.1]octane system, which is of relevance because it can be found as a structural fragment of the zaragozic acids. The fact that these are one-pot domino processes enhances their interest in the context of the current bid for the development of multi-bond-forming reactions as a strategy towards reducing the need for purification processes and hence to increased synthetic efficiency.[12,13]

Experimental section

All reagents (Aldrich, Fluka, SDS, Probus) and solvents (SDS) were of commercial quality and were used as received. Reactions were monitored by thin layer chromatography, on aluminium plates coated with silica gel with a fluorescent indicator (SDS CCM221254). Separations by flash chromatography were performed on silica gel (SDS 60 ACC 40–63 μm). Melting points were measured on a Reichert 723 hot stage microscope, and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Paragon 1000 FT-IR spectrophotometer, with all compounds examined as thin films on NaCl disks. NMR spectra were obtained on Bruker Avance 250 and 500 spectrometers operating at 250 and 500 MHz for ^{1}H and at 63 and 125 MHz for ^{13}C, respectively (CAI de Resonancia Magnética Nuclear, Universidad Complutense). Elemental analyses were determined by the CAI de Microanálisis Elemental, Universidad Complutense, using a Leco 932 CHNS combustion microanalyzer. The bicyclic starting materials were prepared following a literature procedure.[5]

(±)-(1*S**,2*S**,3*R**,5*R**,*S**)-3-Butyl-2-hydroxy-5-nitrocyclo-tetradecanecarboxylic acid (2)

To a solution of compound **1** (0.15 g; 0.45 mmol) in methanol (5 mL), a solution of K_2CO_3 (0.04 g; 0.27 mmol) in water (1 mL) was added. The reaction mixture was stirred at room

temperature for 7 days and poured on water (40 mL), which was extracted with ethyl acetate (2 × 40 mL). The aqueous layer was acidified with 2 M aqueous HCl and extracted again with ethyl acetate (3 × 50 mL). The combined organic layers from the second extraction were dried (Na_2SO_4) and evaporated, and the residue was chromatographed on silica gel, eluting with chloroform followed by diethyl ether, to yield 60 mg (35%) of compound **2**, as a pale yellow oil that was characterized as a 1 : 1 mixture of diastereomers accompanied by the corresponding *aci* tautomer in variable amounts, depending on concentration. IR (neat): 3355 (OH); 2991 (CH); 1706 (CO); 1558 (NO_2); 1464 (C═N_{aci}); 1336 (NO_2) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 8.51 (br s, 3H, 3 COOH); 4.81–4.75 (m, 2H, H-5_{nitro}); 3.87–3.82 (m, 3H, 3 H-2); 3.04–2.94 (m, 3H, 3 H-1); 2.69–2.00 (m, 11H, 2 + 2 H-4_{nitro}, 2 + 2 H-6_{nitro}, 3 OH); 1.90–0.89 (m, 28H$_{aci}$ and 46H$_{nitro}$: H-4_{aci}, H-6_{aci}, NOH$_{aci}$, H-3, H-7–14, $CH_2CH_2CH_2CH_3$); 0.90–0.84 (m, 9H, 3 CH_3) ppm. ^{13}C-NMR ($CDCl_3$, 63 MHz) δ: 180.5, 179.5 and 178.5 (3 COOH); 161.9 (C-5_{aci}); 77.2 and 76.9 (C-5_{nitro}); 71.0, 70.0 and 68.5 (C-2); 48.3, 48.1 and 45.7 (C-1); 37.4, 36.9 and 36.4 (C-3); 34.3; 33.9; 31.6; 31.2; 30.9; 30.5; 30.3; 30.1; 30.0; 29.8; 29.5; 29.3; 29.1 (2 C); 29.0; 28.9; 28.8; 28.7; 28.6; 28.2; 28.0; 27.7; 26.6; 26.3; 26.2; 25.9; 25.8; 25.7; 25.3; 25.0; 24.6; 23.6; 23.4; 23.2; 23.1; 22.9; 22.5; 22.1; 21.2 (C-4, C-6–14, $CH_2CH_2CH_2CH_3$); 14.1, 14.0 and 13.9 (3 CH_3) ppm. Anal. Calcd for $C_{19}H_{35}NO_5$, M = 357: C, 63.84; H, 9.87; N, 3.92. Found: C, 64.03; H, 9.62; N, 3.82.

General procedures for the retro-Dieckmann/reduction sequences

Method A: Reductions employing $LiAlH_4$. To a solution of the suitable bicyclic starting material (1 mmol) in THF (10 mL) was added solid $LiAlH_4$ (5 equiv.) portionwise over 5 min, and the suspension was stirred at room temperature for 24 h. The reaction mixture was cooled in an ice bath and treated dropwise with ethyl acetate (10 mL) and a few drops of water. Solid K_2CO_3 was added and, after energetic stirring, the solid was filtered off. The filtrate was mixed with water (10 mL) and the resulting solution was extracted with CH_2Cl_2 (4 × 20 mL). The combined organic layers were dried (Na_2SO_4) and the residue was purified by chromatography on silica gel, eluting with $CHCl_3$, followed by ethyl acetate, to give the pure compounds **3a** and **3d**.

Method B: Reductions employing $NaBH_4$. To a solution of the suitable bicyclic starting material (1 mmol) in acetonitrile–water (3 : 2, 10 mL) was added portionwise $NaBH_4$ (5 equiv.) over 5 min. The reaction mixture was stirred at room temperature for 3 h and poured on water (10 mL), which was extracted with CH_2Cl_2 (4 × 20 mL). The combined organic layers were dried (Na_2SO_4) and evaporated, to yield the pure compounds **3b,c**.

(+)-(1*S**,2*R**,10*R***S**,11*S**)-2-Hydroxymethyl-11-methyl-10-nitrocyclododecanol (3a)

Yield, 69%, as a 4.5 : 1 mixture of diastereomers a : b. IR (NaCl) *v*: 3360 (OH); 2937; 1545 and 1372 (NO_2) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 4.70–4.50 (m, 1H, H-10, b); 4.48–4.35 (m, 1H, H-10, a); 4.10–3.97 (m, 2H, H-1, a and b); 3.92–3.50 (m, 8H, CH_2OH, 2 OH, a and b); 2.43–0.78 (m, 18H a, 18H b), 1.2 (d, 3H, J = 2.5 Hz, CH_3 a), 0.99 (d, 3H, J = 2.5 Hz, CH_3 b) ppm. ^{13}C-NMR ($CDCl_3$, 63 MHz) δ: 92.4 (C-10, a); 88.2 (C-10, b); 76.2 (C-1 a); 71.0 (C-1 b); 65.8 (CH_2OH a); 65.2 (CH_2OH b); 41.1 (C-11 a); 40.0 (C-11 b); 30.6 (C-2 b); 30.1 (C-2 a); 38.7 (b); 34.0 (a); 29.1 (b); 26.8 (b); 26.6 (a); 26.1 (b); 25.2 (a); 24.7 (b); 24.4 (a); 23.8 (a); 23.7 (a); 23.3 (b); 22.8 (b); 22.3 (a); 22.0 (b); 21.9 (a) (C-3–9, a and b, C-12, a and b); 20.4 (CH_3, a); 16.5 (CH_3, b) ppm. Anal. Calcd for $C_{14}H_{27}NO_4$, M = 273: C, 61.51; H, 9.96; N, 5.12. Found: C, 61.22; H, 9.68; N, 5.06.

(+)-(1*S**,2*R**,4*R***S**,13*R**)-2-Butyl-13-hydroxymethyl-4-nitrocyclotridecanol (3b)

Yield, 85%, as a 1 : 1 mixture of diastereomers a : b. IR (NaCl) *v*: 3383 (OH), 2931, 2861, 1550 and 1376 (NO_2) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 4.52–4.40 (m, 2H, H-4 a and b); 4.02–3.74 (m, 6H, H-1, CH_2OH, a and b); 2.19–2.06 and 1.90–1.82 (2 m, 2H and 6H, H-3, 5 a and b); 1.60–1.10 (m, 48H, H-2 a and b, H-6–13 a and b, 2 OH a and b, $CH_2CH_2CH_2CH_3$ a and b); 0.94–0.87 (m, 6H, CH_3 a and b) ppm. ^{13}C-NMR ($CDCl_3$, 125 MHz) δ: 87.0 (C-4); 84.5 (C-4); 80.3 (C-1); 76.4 (C-1); 66.2 (CH_2OH); 63.9 (CH_2OH); 37.9 (C-13); 37.4 (C-13); 36.4 (C-2); 35.9 (C-2); 36.3; 34.5; 31.3; 29.9; 29.6; 29.5; 29.0; 27.3; 27.1; 27.0; 25.6; 25.2; 25.0; 24.5; 24.3; 23.3; 23.2; 23.1; 23.0; 22.9 (2 C); 22.8; 22.6; 21.6 (C-3, 5–12, $CH_2CH_2CH_2CH_3$); 14.1 (CH_3); 14.0 (CH_3) ppm. Anal. Calcd for $C_{18}H_{35}NO_4$, M = 329: C, 65.62; H, 10.71; N, 4.25. Found: C, 65.50; H, 10.45; N, 4.03.

(+)-(1*S**,2*R**,4*R***S**,14*R**)-2-Butyl-14-hydroxymethyl-4-nitrocyclotetradecanol (3c)

Yield, 65%, as a 2 : 1 mixture of diastereomers a : b. IR (NaCl) *v*: 3399 (OH); 1552 (NO_2); 1462; 1345 (NO_2) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 4.62–4.45 (m, 2H, H-4 a and b); 4.10–3.53 (m, 10H, H-1, CH_2OH, 2 OH a and b); 2.30–1.72 (m, 12H, H-2, 3, 5, 14 a and b); 1.71–1.00 (m, 44H, H-6–13, $CH_2CH_2CH_2CH_3$ a and b); 1.00–0.80 (m, 6H, CH_3 a and b) ppm. ^{13}C-NMR ($CDCl_3$, 63 MHz) δ: 86.6 (C-4 a); 85.8 (C-4 b); 80.1 (C-1 a); 77.2 (C-1 b); 67.0 (CH_2OH b); 66.1 (CH_2OH a); 42.1 (C-14 a); 39.8 (C-14 b); 37.6 (C-2 a); 36.6 (C-2 b); 35.7 (a); 34.1 (b); 30.4 (a); 30.1 (a); 30.0 (b); 29.9 (b); 28.3 (b); 28.0 (b); 26.6 (b); 26.4 (a); 26.4 (a); 25.7 (b); 25.2 (a); 25.0 (a); 24.8 (b); 24.7 (b); 24.3 (a); 24.2 (a); 23.3 (a); 23.2 (a); 22.9 (b); 22.8 (b); 22.4 (b); 22.2 (b); 21.2 (a); 21.0 (a) (C-3 a and b, C-5–13, a and b, $CH_2CH_2CH_2CH_3$ a and b); 14.0 (CH_3, a); 13.9 (CH_3, b) ppm. Anal. Calcd for $C_{19}H_{37}NO_4$, M = 343: C, 66.43; H, 10.86; N, 4.08. Found: C, 60.10; H, 11.02; N, 3.80.

(+)-(1*S**,2*R**,12*R***S**,13*S**)-2-Hydroxymethyl-13-methyl-12-nitrocyclotetradecanol (3d)

Yield, 37%, as a 1.3 : 1 diastereomer mixture a : b. IR (NaCl) *v*: 3362 (OH); 2961; 1525 (NO_2); 1461; 1341 (NO_2) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 4.70–4.42 (br s, 6H, H-12, 2 OH a and b); 4.06–3.59 (m, 6H, H-1, CH_2OH, a and b);

2.56–0.81 (m, 50H, H-2–11, 13, 14, CH_3 a and b) ppm. ^{13}C-NMR ($CDCl_3$, 63 MHz) δ: 78.4 (C-12); 78.2 (C-12); 72.3 (C-1); 70.2 (C-1); 63.0 (CH_2OH); 63.0 (CH_2OH); 43.3 (C-2); 42.8 (C-2); 34.8 (C-13); 33.0 (C-13); 39.9; 39.2; 35.0; 29.8; 29.7; 27.2; 26.8; 26.6; 26.2; 26.0; 25.9; 25.5; 25.4; 25.1; 24.7; 24.6; 24.5; 24.3; 24.0; 23.5 (C-3–11, C-14); 18.9 (CH_3); 11.9 (CH_3) ppm. Anal. Calcd for $C_{16}H_{31}NO_4$, M = 301: C, 63.75; H, 10.37; N, 4.65.

General procedure for the retro-Dieckmann/reduction/Nef and retro-Dieckmann/reduction/Nef/cyclic ketalization reactions

To a solution of the suitable bicyclic starting material (1 mmol) in acetonitrile–water (3 : 2, 10 mL) was added portionwise $NaBH_4$ (5 equiv.) over 5 min. The reaction mixture was stirred at room temperature for 5–24 h and, if the reaction was not finished as judged by TLC, an additional amount of reducing agent (5 equiv.) was added as described above. If necessary, the same addition can be repeated 24 h later. When the reduction step was complete, the reaction medium was acidified with 2 M or 4 M aqueous HCl (10 mL) and stirred at room temperature for the time specified in Table 2. The reaction mixture was extracted with CH_2Cl_2 (4 × 20 mL), and the combined organic layers were dried over Na_2SO_4 and evaporated. The residue was purified by chromatography on silica gel, with 9 : 1 petroleum ether–CH_2Cl_2. Alternatively, for the reactions carried out at 3 mmol or higher scale, the crude compounds **5** were dissolved in a mixture of ethanol (20 mL) and 37% aqueous HCl (0.2 mL), and the solution was stirred at room temperature for 12 h and diluted with saturated aqueous $NaHCO_3$ (30 mL) and CH_2Cl_2 (30 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were dried over Na_2SO_4 and evaporated, and the residue was purified as indicated above, giving compounds **6**.

(±)-(4*S**,5*R**)-5-Hydroxymethyl-4-hydroxycyclododecanone (5a)

Yield, 62%. IR (NaCl) ν: 3285 (OH), 2930, 1705 (CO), 1467, 1031 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 3.83–3.76 (m, 2H, H-4, CH_2OH); 3.65 (dd, 1H, J = 5.3 and 2.3 Hz, CH_2OH); 2.92 (ddd, 1H, J = 8.6, 5.9 and 1.5 Hz); 2.60–2.56 (m, 2H); 2.25–2.18 (m, 1H); 2.11–1.98 (m, 3H); 1.91–1.05 (m, 14H) ppm. ^{13}C-NMR ($CDCl_3$, 125 MHz) δ: 212.9 (C-1); 71.8 (C-4); 65.4 (CH_2OH); 43.8 (C-5); 40.1 and 38.3 (C-2 and C-12); 27.5; 26.1; 24.7; 23.2; 22.8; 22.8; 22.0 (C-3, 6–11) ppm. Anal. Calcd for $C_{13}H_{24}O_3$, M = 228: C, 68.38; H, 10.59. Found: C, 68.09; H, 10.66.

(±)-(3*R**,4*S**,5*R**)-5-Hydroxymethyl-4-hydroxy-3-methyl-cyclododecanone (5b)

Yield, 80%. IR (NaCl) ν: 3396 (OH), 2930, 1705 (CO), 1418, 1338, 1031 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 4.08–3.20 (m, 5H, H-4, CH_2OH, 2 OH); 3.15–2.86 (m, 1H); 2.80–2.63 (m, 1H); 2.60–0.66 (m, 19H) ppm. ^{13}C-NMR ($CDCl_3$, 125 MHz) δ: 211.5 (C-1); 84.9 (C-4); 65.7 (CH_2OH); 35.8 (C-5); 32.5 (C-3); 34.4 and 31.1 (C-2 and C-12); 29.6; 28.0; 24.1; 23.7; 22.8; 21.6 (C-6–11); 14.2 (CH_3) ppm. Anal. Calcd for $C_{14}H_{26}O_3$, M = 242: C, 69.38; H, 10.81. Found: C, 69.02; H, 10.53.

(±)-(2*R**,4*S**,5*R**)-5-Hydroxymethyl-4-hydroxy-2-methyl-cyclododecanone (5c)

Yield, 84%, as a 1 : 1 mixture of diastereomers a : b. IR (NaCl) ν: 3435 (OH), 2931, 1704 (CO), 1419, 1338 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 4.33–3.40 (m, 6H, H-4, CH_2OH a and b); 2.90–0.85 (m, 46H) ppm. ^{13}C-NMR ($CDCl_3$, 63 MHz) δ: 215.2 (C-1); 214.7 (C-1); 80.6 (C-4); 80.2 (C-4); 65.0 (CH_2OH); 64.6 (CH_2OH); 44.1 (C-5); 42.5 (C-5); 40.5 (C-2); 40.2 (C-12); 36.6 (C-2); 39.8 (C-12); 38.5; 36.0; 32.8; 26.5; 26.3; 26.1; 25.7; 24.9; 24.0; 23.5; 22.8; 22.1; 21.3; 20.3 (C-3, 6–11); 17.3 (CH_3); 13.5 (CH_3) ppm. Anal. Calcd for $C_{14}H_{26}O_3$, M = 242: C, 69.38; H, 10.81. Found: C, 69.10; H, 10.44.

(±)-(4*S**,5*R**)-5-Hydroxymethyl-4-hydroxycyclotridecanone (5d)

Yield, 51%. IR (NaCl) ν: 3378 (OH), 2926; 1715 (CO), 1418, 1045 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 4.23–3.65 (m, 5H, H-4, CH_2OH, 2 OH); 2.60–0.85 (m, 21H) ppm. ^{13}C-NMR ($CDCl_3$, 63 MHz) δ: 213.8 (C-1); 70.7 (C-4); 64.5 (CH_2OH); 41.2 (C-5); 34.0 and 30.9 (C-2 and C-13); 28.6; 27.9; 25.3; 25.0; 24.8; 23.6; 21.7; 21.6 (C-3, 6–12) ppm. Anal. Calcd for $C_{14}H_{26}O_3$, M = 242: C, 69.38; H, 10.81. Found: C, 69.09; H, 10.66.

(±)-(3*R**,4*S**,5*R**)-5-Hydroxymethyl-4-hydroxy-3-methylcyclotridecanone (5e)

Yield, 64%. IR (NaCl) ν: 3359 (OH), 2929, 1708 (CO), 1462, 1044 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 3.84–3.60 (m, 3H, H-4, CH_2OH); 2.60–2.40 (m, 2H); 2.35–2.27 (m, 1H); 2.27–2.16 (m, 1H); 1.89–0.87 (m, 21H) ppm. ^{13}C-NMR ($CDCl_3$, 125 MHz) δ: 212.2 (C-1); 77.0 (C-4); 65.6 (CH_2OH); 40.7 (C-5); 33.2 (C-3); 48.2 and 41.4 (C-2 and C-13); 27.6; 26.1; 25.9; 24.9; 24.8; 22.2; 22.0 (C-6–12); 15.1 (CH_3) ppm. Anal. Calcd for $C_{15}H_{28}O_3$, M = 256: C, 70.27; H, 11.01. Found: C, 70.02; H, 10.76.

(±)-(2*R**,4*S**,5*R**)-5-Hydroxymethyl-4-hydroxy-2-methyl-cyclotridecanone (5f)

Yield, 56% as a 2 : 1 mixture of diastereomers. Data for the major diastereomer, purified by silica gel column chromatography, eluting with a gradient from petroleum ether to dichloromethane: IR (NaCl) ν: 3401 (OH), 2930, 1709 (CO), 1416, 1342, 1054 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 3.96 (dd, 1H, J = 16.1 and 3.1 Hz; CH_2OH); 3.78–3.49 (m, 4H, H-4, CH_2OH, 2 OH); 3.10–2.85 (m, 1H); 2.80–2.61 (m, 2H); 2.46–2.23 (m, 3H); 2.10–0.80 (m, 17H) ppm. ^{13}C-NMR ($CDCl_3$, 63 MHz) δ: 217.1 (C-1); 71.4 (C-4); 65.1 (CH_2OH); 43.8 (C-5); 42.0 (C-2); 42.6 (C-13); 41.0; 26.8; 26.4; 25.8; 24.6; 24.0; 23.2; 22.2 (C-3, 6–12); 18.4 (CH_3) ppm. Anal. Calcd for $C_{15}H_{28}O_3$, M = 256: C, 70.27; H, 11.01. Found: C, 70.01; H, 10.68.

(±)-(3*R,4*S**,5*R**)-5-Hydroxymethyl-4-hydroxy-3-methyl-cyclotetradecanone (5g)**

Yield, 100%. IR (NaCl) *v*: 3355 (OH), 2931, 1710 (CO), 1461, 1045 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 250 MHz) *δ*: 4.75–3.46 (m, 5H, H-4, C*H*$_2$OH, 2 OH); 2.81–0.63 (m, 22H), 0.98 (d, 3H, *J* = 6.7 Hz, CH_3) ppm. ^{13}C-NMR ($CDCl_3$, 125 MHz) *δ*: 213.1 (C-1); 78.8 (C-4); 66.2 (*C*H$_2$OH); 48.5 (C-5); 40.7 (C-3); 40.4 and 33.4 (C-2 and C-14); 28.3; 26.5; 26.4; 25.6; 25.0; 24.3; 22.3; 21.7 (C-6–13); 14.7 (CH_3) ppm. Anal. Calcd for $C_{16}H_{30}O_3$, *M* = 270: C, 71.07; H, 11.18. C, 71.11; H, 11.11. Found: C, 70.98; H, 10.86.

(±)-(1*S,11*R**,12*R**)-1,12-Epoxy-15-oxabicyclo[9.3.2]hexadecane (6g)**

Yield, 100%. IR (NaCl) *v*: 2924, 1463, 1263, 1063 (C–O) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 250 MHz) *δ*: 4.37 (d, 1H, *J* = 6.8 Hz, H-12); 4.05 (dd, 1H, *J* = 11.8 and 4.0 Hz, H-16); 3.74 (d, 1H, *J* = 11.8 Hz, H-16); 2.20–0.85 (m, 23H) ppm. ^{13}C-NMR ($CDCl_3$, 63 MHz) *δ*: 106.3 (C-1); 79.3 (C-12); 62.7 (C-16); 36.9 (C-11); 36.3 and 35.4 (C-2 and C-14); 29.6; 28.7; 28.0; 27.0; 26.2; 25.4; 23.5; 23.1; 22.0 (C-3–10, 13) ppm. Anal. Calcd for $C_{15}H_{26}O_2$, *M* = 238: C, 75.58; H, 10.99. Found: C, 75.20; H, 10.55.

(±)-(1*S,11*R**,12*R**,13*S**)-1,12-Epoxy-13-methyl-15-oxabicyclo-[9.3.2]hexadecane (6h)**

Yield, 94%. IR (NaCl) *v*: 2927, 1462, 1272, 1061 (C–O) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 250 MHz) *δ*: 4.08–4.01 (m, 2H, H-12, 16); 3.75 (dd, 1H, *J* = 11.9 and 1.2 Hz, H-16); 2.58–2.43 (m, 1H); 2.08 (dd, 1H, *J* = 13.3 and 11.8 Hz); 1.98–1.25 (m, 20H); 1.12 (d, 3H, *J* = 7.2 Hz, CH_3) ppm. ^{13}C-NMR ($CDCl_3$, 63 MHz) *δ*: 106.5 (C-1); 82.7 (C-12); 63.1 (C-16); 34.5 (C-11); 31.1 (C-13); 42.8 and 37.2 (C-2 and C-14); 31.2; 28.3; 27.6; 27.3; 25.9; 24.0; 23.4; 21.6 (C-3–10); 12.6 (CH_3) ppm. Anal. Calcd for $C_{16}H_{28}O_2$, *M* = 252: C, 76.14; H, 11.18. Found: C, 75.92; H, 10.99.

(±)-(1*S,11*R**,12*R**,13*S**)-13-Butyl-1,12-epoxy-15-oxabicyclo-[9.3.2]hexadecane (6i)**

Yield, 90%. IR (NaCl) *v*: 2927, 1462, 1279, 1065 (C–O) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 250 MHz) *δ*: 4.09–3.94 (m, 1H, H-16); 3.74–3.66 (m, 2H, H-12, 16); 2.49–0.88 (m, 31H) ppm. ^{13}C-NMR ($CDCl_3$, 63 MHz) *δ*: 106.1 (C-1); 81.9 (C-12); 63.3 (C-16); 40.8 (C-11); 31.2 (C-13); 41.3 and 37.2 (C-2 and C-14); 31.4; 31.3; 28.2; 27.9; 27.6; 27.3; 25.9; 24.0; 23.4; 22.8; 21.5 (C-3–10, *C*H$_2$*C*H$_2$*C*H$_2$CH$_3$); 14.0 (CH_3) ppm. Anal. Calcd for $C_{19}H_{34}O_2$, *M* = 294: C, 77.50; H, 11.64. Found: C, 77.21; H, 11.45.

(±)-(1*S,11*R**,12*R**,14*R**,*S**)-1,12-Epoxy-14-methyl-15-oxabicyclo-[9.3.2]hexadecane (6j)**

Yield, 99%, as a 1 : 1 mixture of diastereomers. IR (NaCl) *v*: 2924, 1109 (C–O) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 250 MHz) *δ*: 4.32–4.26 (m, 2H, H-12); 4.14 (dd, 1H, *J* = 11.7 and 4.5 Hz, H-16); 4.05 (dd, 1H, *J* = 11.8 and 4.0 Hz, H-16); 3.75 (dt, 2H, *J* = 11.7 and 1.4 Hz, H-16); 2.62–2.40 (m, 2H); 2.12–1.21 (m, 42H); 1.14 (d, 3H, *J* = 7.2 Hz, CH_3); 0.97 (d, 3H, *J* = 7.0 Hz, CH_3) ppm. ^{13}C-NMR ($CDCl_3$, 63 MHz) *δ*: 107.4 (C-1); 106.2 (C-1); 77.8 (C-12); 77.84 (C-12); 62.6 (C-16); 61.5 (C-16); 42.4 (C-11); 40.1 (C-11); 36.8 (C-14); 36.5 (C-14); 37.7 (C-2); 35.6 (C-2); 34.6; 32.7; 28.6; 28.19; 28.15; 27.7; 27.0 (2 C); 26.0; 25.9; 25.5; 25.4; 23.74; 23.72; 23.3; 23.0; 22.1; 22.0 (C-3–10, 13); 19.1 (CH_3); 12.6 (CH_3) ppm. Anal. Calcd for $C_{16}H_{28}O_2$, *M* = 252: C, 76.14; H, 11.18. Found: C, 76.03; H, 11.05.

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Notes and references

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