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A General Synthesis of Bis-α-acyloxy-1,4- and -1,5-diketones Through Catalytic Oxidative Opening of Acylated THF and THP Diols

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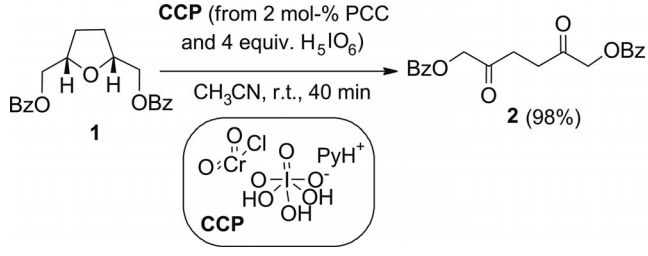
The first general synthesis of bis-α-acyloxy-1,4- and -1,5-diketones has been accomplished in a catalytic oxidative opening of bis-acylated THF and THP (tetrahydropyran) diols, which were synthesised by osmium- or ruthenium-catalysed oxidative cyclisation of 1,5- and 1,6-dienes. The overall sequence corresponds to the regioselective double ketoacyloxylation of the starting diene. The synthesised bis-α-acyloxy-1,5-dicarbonyl compounds have been transformed into pyridine-based oxido pincer ligands or pyrazinedimethanol substances, leading to the discovery of unprecedented aromatisation routes.

Introduction

α-Acyloxy ketones are important intermediates in organic synthesis, and their structural motif is found in a variety of natural products (e.g., taxol) and pharmaceutical agents. They can be seen as protected α-hydroxy ketones, themselves structural subunits of several active natural substances and useful synthetic building blocks.[1]

The keen interest of synthetic organic chemists in α-acyloxy ketones is demonstrated by the number of procedures that have been developed to obtain these substances.[2] Generally, their synthesis features the introduction of the acyloxy group α to the ketone functional group. Recently, various asymmetric α-oxybenzoylation methods have been reported.[3] A thallium-promoted preparation of α-formyloxy ketones is also known.[2f] However, despite the potential uses of the products in organic synthesis, to the best of our knowledge, no general method for the synthesis of bis-α-acyloxy diketones has been developed to date, and the chemistry of these compounds and that of the corresponding free bis-ketols is still largely unexplored.[4]

Recent work in our laboratory has focussed on the catalytic use of chlorochromatoperiodate (CCP, Scheme 1), generated by the condensation of PCC (pyridinium chlorochromate) and periodic acid,[5] as a powerful reagent capable of oxidising THF-containing compounds of varying structural complexity.[6] In a single case, we observed that the oxidative opening of 2,5-bis-benzoyloxymethyl THF derivative **1** (Scheme 1) led to bis-α-benzoyloxy 1,4-diketone **2** in an excellent yield.



Scheme 1. Oxidative THF opening under previous conditions.[6]

This result was particularly interesting, since it suggested that THF rings, and possibly other ether rings flanked by acylated hydroxymethyl groups, could be seen as masked bis-α-acyloxy diketones. With the above result in mind, we envisaged that 1,5- and 1,6-dienes could be transformed into bis-α-acyloxy-1,4- and -1,5-diketones through a short sequence consisting of transition-metal-mediated oxidative cyclisation of the diene[7] to give THF or THP diols, followed by hydroxyl acylation, and CCP-catalysed opening of the ether ring (Scheme 2).

Since the formation of the two ketone functionalities occurs at the ether carbons, the projected sequence should allow the bis-ketoacyloxylation of the starting diene to occur regioselectively, which is hardly achievable in a direct way. In a previous investigation by Smith III and Scarborough,[8] the system RuO_2 (cat.)/$NaIO_4$ was used to accomplish the oxidation of unfunctionalised THF or THP rings, mostly to give lactones. In a single case, a 2,5-disub-

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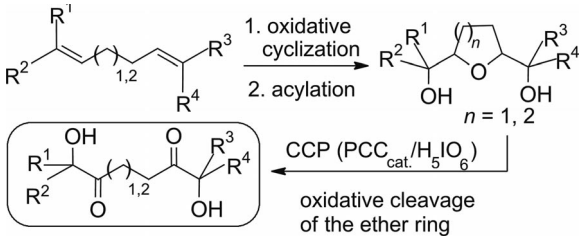


Scheme 2. Projected general synthesis of bis-α-acyloxy diketones from dienes.

stituted THF was converted into a 1,4-diketone, but the process required long reaction times (typically 24 h), and there were no chiral centres adjacent to the reaction centre. In this paper, we report the accomplishment of the above idea and the use of some of the synthesised 1,5-diketones to obtain six-membered nitrogen heterocycles.

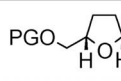
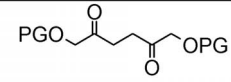
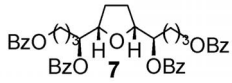
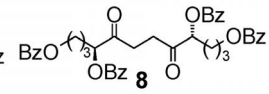
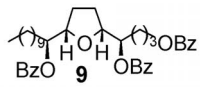
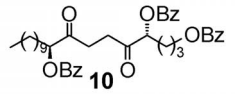
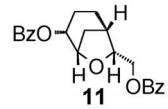
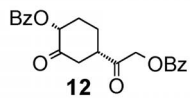
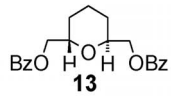
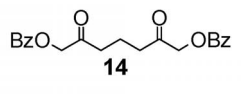
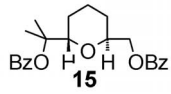
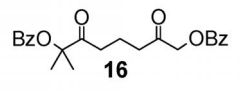
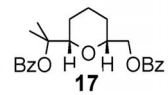
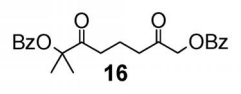
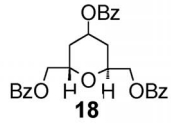
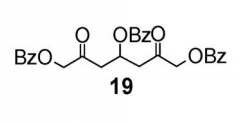
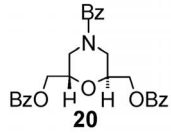
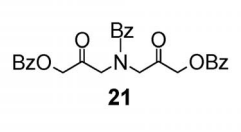
Results and Discussion

To test the substrate scope of the projected transformation, a range of tetrahydrofuran and tetrahydropyran diols were synthesised, mostly through well-established ruthenium[9] or osmium[10]-catalysed oxidative cyclisation of suitable 1,5- and 1,6-dienes. The diols were then acylated (or in one case tosylated) and subjected to our oxidative procedure (Table 1).

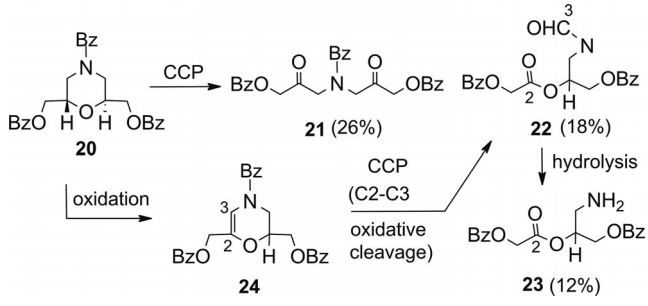
Optimisation of the oxidative protocol was carried out with THF **1** and THP **13** as model compounds. We found that the oxidation of **1** (entry 1, Table 1) proceeded in excellent yields and short reaction times with 2 mol-% of PCC, even when the amount of the co-oxidant was reduced to 3 equiv. However, the opening of the THP ring of **13** proceeded very slowly or the reaction was incomplete under these conditions. A screening of the reaction conditions for this substrate showed that the best results were obtained with 4 mol-% of catalyst and 4 equiv. of periodic acid.

Oxidation of all the other substrates was then carried out under the optimised conditions. As summarised in Table 1, both THF and THP derivatives reacted well to give the expected diketones in generally good to excellent yields.[11] The process was shown to be tolerant of various substitution patterns and of structural complexity in the substrate. Even bicyclic THF **11** (entry 6) gave a good yield of the corresponding diketone **12**. Isomeric *trans* and *cis*[9d] THPs **15** and **17**, respectively (entries 8 and 9), gave the same product **16** in comparable yields. In an attempt to further expand the utility of this reaction, morpholine derivative **20** (entry 11, Scheme 3) was oxidised. However, a more complex reactivity pattern resulted in this case. The expected diketone (i.e., **21**) was obtained, albeit in a diminished 26% yield (HPLC),[12] along with a non-negligible amount of byproducts **22** (18%) and **23** (12%). We believe that the Achilles' heel of this substrate is the double bond character of the benzamide group, which favours the formation of unsaturated morpholine intermediate **24**, which is then oxidatively cleaved by CCP itself (Scheme 3).[13] Presumably,

Table 1. CCP-catalysed oxidative opening of protected 2,5-disubstituted THF and 2,6-disubstituted THP diols.[a]

Entry	Substrate	Product	Yield (%)[c]
1			
	1 (PG = Bz)	**2**	97
2	**3** (PG = Ac)	**4**	80
3[b]	**5** (PG = Ts)	**6**	85
4			74
5			61
6			75
7			85
8			95
9			83
10			78
11			26[d]

[a] Reagents and conditions. THF oxidations: substrate (0.05 M in CH_3CN), PCC (2 mol-%), H_5IO_6 (3.2 equiv.), 30–40 min, room temp. THP oxidations: substrate (0.05 M in CH_3CN), PCC (4 mol-%), H_5IO_6 (4 equiv.), 6–8 h, room temp. [b] This process required 24 h. [c] Isolated yields. [d] Isolated HPLC yield.



Scheme 3. Oxidation of a morpholine-protected substrate. Reaction conditions as in Table 1.

higher yields of compounds corresponding to **21** could be obtained by tuning the nitrogen-protecting group in **20**. As can be seen, benzoate (entry 1), acetate, tosylate (entries 2 and 3), and amide functionalities (entry 11) were compatible with the ether-cleavage reaction conditions.

An important aspect of the process that must be addressed concerns the fate of the potentially epimerisable chiral centers adjacent to the newly-formed ketone functionalities in compounds such as **8**, **10**, and **12**. Considering the oxidation of **11**, NMR spectroscopic analysis of the by-products of the process ruled out the presence of stereoisomers of diketone **12**. In addition, an X-ray diffraction analysis of this compound (Figure 1)[14] was carried out, and the results showed that the relative stereochemistry of THF precursor **11** had been preserved in **12**. This suggests that the synthesis of chiral, acyclic bis-α-acyloxy-1,4-diketones such as **8** and **10** is feasible, given the easy access to chiral THF-dimethanol substances such as **7** or **9** according to the OsO_4-catalysed protocol developed by Donohoe and Butterworth.[15]

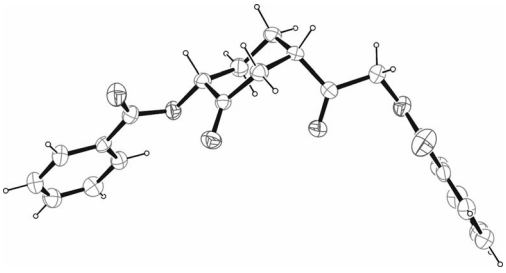
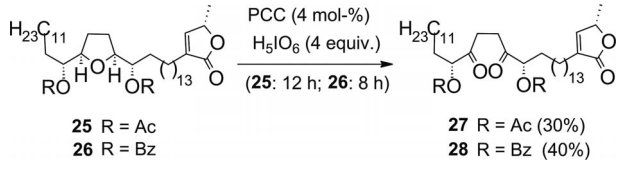


Figure 1. ORTEP drawing of diketone **12**. Ellipsoids are drawn at the 30% probability level.

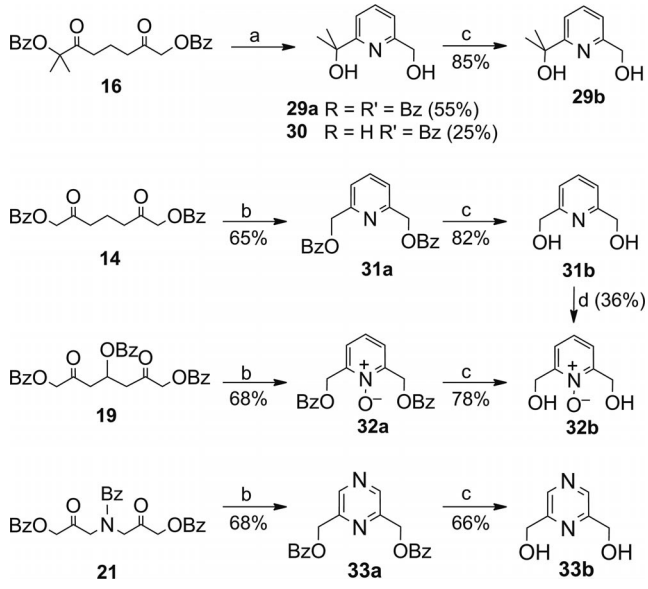
To test our procedure on a more elaborate substrate, acetylated and benzoylated *cis*-reticulatacins **25** and **26**, respectively, were oxidised (Scheme 4).[16,17] *cis*-Reticulatacin belongs to the *Annonaceous* acetogenins class, a group of plant-derived metabolites having a wide array of biological properties such as antitumor, immunosuppressive, antimicrobial, and insecticidal activities.[18] Several syntheses of some members of this group as well as the preparation of analogues have been reported.[19] We envisaged that our process could be used to cleave the THF ring in this compound to obtain non-THF analogues such as recently synthesised dihydro-coibin[20] or other derivatives thereof.



Scheme 4. Oxidation of bis-acylated *cis*-reticulatacin.

Indeed, the reaction of **25** and **26** under slightly modified conditions gave the expected reticulatacin-derived diketones (i.e., **27** and **28**, respectively; Scheme 4) albeit in lower yields (30–40%). Although the structures of the by-products (HPLC separation) of this process were not thoroughly investigated, ^1H NMR spectroscopic data showed that they all incorporated the terminal unsaturated lactone functionality (characteristic proton signals at ca. 5 and 7 ppm), which indicates that even this moiety is tolerant to the oxidising conditions. This transformation also highlights that the method may be useful to prepare analogues of a variety of biologically active natural substances, where saturated ether rings of various sizes are often flanked by hydroxy groups.

It is well known[1b,2] that α-oxygenated carbonyl groups are susceptible to several transformations. The presence in the same molecule of two of these structural subunits further increases the synthetic utility of these compounds. Among the various conceivable synthetic uses of the synthesised substances, we planned to probe the transformation of the 1,5-dicarbonyl compounds into the corresponding pyridinedimethanol derivatives[21,22] (Scheme 5). These substances have notable coordination properties, and belong to the oxido pincer ligands class.[23]



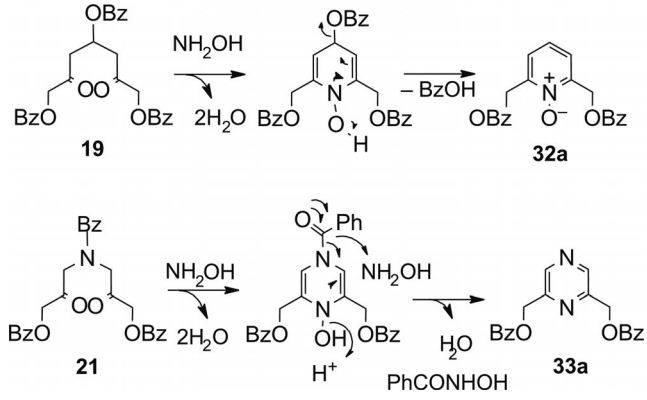
Scheme 5. Pyridine and pyrazine diol synthesis from bis-α-benzoyloxy 1,5-diketones. a) NH_4OAc (7 equiv.), AcOH (6.5 equiv.), dry MeOH, 24 h room temp. and 48 h 55 °C; b) $NH_2OH{\cdot}HCl$ (3.5 equiv.), dry EtOH, 6–15 h, reflux; c) K_2CO_3 (10 mol-%), MeOH, room temp., 30 min; d) MCPBA (1.2 equiv.), $CHCl_3$, room temp., 90 min.

Reaction of **16** with ammonium acetate and AcOH gave, in a reproducible manner, the expected pyridine (i.e., **29a**) together with the corresponding debenzoylated compound (i.e., **30**) in a ca 2:1 ratio. Usually, it is believed that under these conditions, 1,4-dihydropyridine intermediates disproportionate to give the pyridine compounds and products with higher hydrogen content such as piperidines or tetrahydropyridines. However, our process was very clean, and no by-products of this type could be detected. Thus, in agreement with Rodriguez et al.,[24] we presume that atmospheric oxygen could be responsible for the oxidation step leading to aromatisation.

Compound **14** failed to cyclise under these conditions. In an alternative approach, good yields of pyridine **31a** were

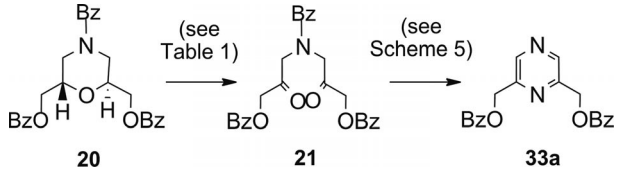
obtained by the reaction of **14** with hydroxylamine hydrochloride under classical Knoevenagel conditions. Analogously, the reaction of diketone **19** under the conditions used to cyclise **14** led to pyridine oxide **32a**. Even diketobenzamide **21** could be cyclised to give 2,6-bis(hydroxymethyl)pyrazine **33a** in good yield and in a short time compared to the pyridine cyclisations. The formation of a pyrazine ring through cyclisation of a diketoamide such as **21** has never been accomplished before, and it is likely that variants of this process will be feasible. Debenzoylation of the mixture of **29a** and **30**,[25] and of compounds **31a**–**33a** was then carried out with K_2CO_3 (cat.) in MeOH to give the corresponding diols. Compounds **29b** and **31b** are known. The structural relationship between **31b** and **32b** was proved by MCPBA (*m*-chloroperbenzoic acid) oxidation of the former to give the latter.

The cyclisations of **19** and **21** are particularly interesting and deserve a comment. As for the transformation of **19** into **32a** (Scheme 6), the benzoate group on C-4 acts as a leaving group and, after formation of the intermediate *N*-hydroxydihydropyridine, aromatisation occurs by elimination of benzoic acid. This is the first example of the synthesis of the pyridine nucleus using a 3-benzoyloxy-1,5-diketone. An interesting new feature of this reaction is the direct formation of a pyridine oxide.



Scheme 6. Plausible pathways leading to pyridine oxide **32a** and pyrazine **33a**.

A pathway leading to pyrazine **33a** is shown in Scheme 6. In this case, the initial closure of the *N*-hydroxydihydropyrazine ring is followed by the elimination of the benzoyl portion, probably through a transamidation step driven by aromatisation. Overall, the oxidative opening of the morpholine ring in **20** to give diketone **21** (Scheme 7), followed by cyclisation of the latter compound to give pyrazine **33a**, i.e., the transformation of a morpholine derivative into a pyrazine, may have synthetic and pharmacological value.[26]



Scheme 7. Overall transformation of morpholine **20** into pyrazine **33a**.

Conclusions

In conclusion, we have developed the first general procedure for the synthesis of bis-α-acyloxy-1,4- and -1,5-diketones from 1,5- and 1,6-dienes, respectively, in a regioselective manner. An interesting feature of our procedure is the timing of the introduction of the acyloxy and ketone functionalities onto the diene, which allows a variety of acyloxy moieties to be incorporated. In addition, it is reasonable to assume that THF or THP substrates that lack one or both of the neighbouring acyloxy groups could be cleaved using our procedure, which would give a wider spectrum of 1,4- and 1,5-diketones. We have demonstrated that the process can be applied to acylated *cis*-reticulatacin, a representative mono-THF *Annonaceous* acetogenin, thus opening the way to the preparation of new non-THF analogues of these active substances to be used in biological assays. The 1,5-diketone products have been successfully cyclised to give pyridinedimethanol derivatives, opening a new route to pyridine-based oxido pincer ligands, and, in one case, to a pyrazinedimethanol derivative. The direct conversion of a 3-benzoyloxy-1,5-diketone into a pyridine *N*-oxide is also unprecedented. The synthetic utility of the bis-α-acyloxy-diketone products is currently under investigation.

Experimental Section

General Methods: All reagents and anhydrous solvents were purchased (Aldrich and Fluka) at the highest commercial quality and were used without further purification. Reactions were monitored by thin-layer chromatography carried out on precoated silica gel plates (Merck 60, F_{254}, 0.25 mm thick). Merck silica gel (Kieselgel 40, particle size 0.063–0.200 mm) was used for column chromatography. Na_2SO_4 was used as a drying agent for aqueous work-up. HPLC separations were carried out with a Varian 2510 apparatus equipped with a Waters R403 dual cell differential refractometer using Phenomenex 250 × 10 mm and 250 × 4.6 mm (both 5 μm) columns. NMR experiments were performed with Varian Unity Inova 700, Varian Unity Inova 500, Varian Mercury Plus 400, and Gemini 200 spectrometers in $CDCl_3$ or CD_3OD. Proton chemical shifts were referenced to the residual $CHCl_3$ (δ = 7.26 ppm) or CD_2HOD (δ = 3.31 ppm) signals. ^{13}C NMR chemical shifts were referenced to the solvents $CDCl_3$ (δ = 77.0 ppm) or CD_3OD (δ = 49.0 ppm). Coupling constants, *J* values, are given in Hz. Abbreviations for signal coupling are as follows: s = singlet, d = doublet, dd = double doublet, ddd = double double doublet, t = triplet, dt = double triplet, q = quartet, quin = quintet, m = multiplet, app = apparent, br. = broad. Optical rotations were recorded with a Jasco P-1010 polarimeter (using the sodium D line, 589 nm) and $[\alpha]_D$ values are given in units of deg cm^3 g^{-1} dm^{-1}. IR spectra were collected with a Jasco FTIR-430 spectrometer. Melting points were obtained with a Gallenkamp melting point apparatus. High Resolution MS were recorded with a Bruker APEX II FT-ICR mass spectrometer using the electrospray ionisation (ESI) technique in positive mode.

Crystals of **12** were grown by slow evaporation from a $CHCl_3$/toluene (1:1) solution. A prismatic colourless crystal of **12** was selected for X-ray analysis. Single crystal X-ray diffraction data were collected using graphite monochromated Mo-K_α radiation (λ = 0.71073 Å) with a Bruker–Nonius kappaCCD diffractometer at room temperature. Owing to the poorly diffracting features of the crystal, data were collected up to θ_{max} = 25°. Unit cell parameters were determined by least-squares refinement of the θ angles of 35 strong reflections in the range 3.785° < θ < 11.308°. Data reduction and semiempirical absorption correction were done using SADABS program.[27] The structure was solved by direct methods (SIR97 program[28]) and refined by the full-matrix least-squares method on F^2 using SHELXL-97 program.[29] All non-hydrogen atoms were refined anisotropically. H atoms were determined stereochemically and refined by the riding model with U_{iso} = 1.2·U_{eq} of the carrier atom.

Synthesis of Substrates: Substrates **1**,[9c] **3**,[9c] **5**,[9c] **7**,[30] **9**,[31] **11**,[32] **13**,[9d] **15**,[9d] **17**,[9d] and **20**[9e] were obtained by acetylation, benzoylation and tosylation of the corresponding THF, THP, or morpholine polyols under standard conditions. The latter compounds were synthesised according to literature procedures. Compound **1**[6] is a known compound. Compound **18** was synthesised from hepta-1,6-dien-4-yl benzoate according to a literature procedure[9e] and benzoylated under standard conditions.

(±)-[(2*S*,5*R*)-Tetrahydrofuran-2,5-diyl]bis(methylene) Diacetate (3): Oil. IR: $\tilde{\nu}$ = 1742 (s), 1372 (w), 1235 (br. s), 1041 (m) cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 4.30–4.06 (m, 4 H), 3.97 (dd, J = 12.3, 7.2 Hz, 2 H), 2.07 (s, 6 H), 2.16–1.89 (m, 2 H), 1.83–1.55 (m, 2 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 170.5, 77.0, 66.1, 27.3, 20.5 ppm. HRMS (ESI): calcd. for $C_{10}H_{16}NaO_5$ [M + Na]$^+$ 239.0895; found 239.0884.

(±)-[(2*S*,5*R*)-Tetrahydrofuran-2,5-diyl]bis(methylene) Bis(4-methylbenzenesulfonate) (5): Oil. IR: $\tilde{\nu}$ = 2957 (m), 2922 (m), 2855 (w), 1597 (w), 1356 (m), 1260 (w), 1189 (m), 1174 (s), 1094 (m), 969 (m), 812 (m), 665 (m) cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 7.77 (d, J = 8.1 Hz, 4 H), 7.34 (d, J = 8.1 Hz, 4 H), 4.17–4.02 (m, 2 H), 3.93 (m, 4 H), 2.45 (s, 6 H), 2.03–1.85 (m, 2 H), 1.84–1.64 (m, 2 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 144.9, 132.8, 129.9, 127.9, 77.2, 71.1, 27.5, 21.6 ppm. HRMS (ESI): calcd. for $C_{20}H_{24}NaO_7S_2$ [M + Na]$^+$ 463.0861; found 463.0859.

(±)-(4*S*)-4-(Benzoyloxy)-4-{(2*S*,5*R*)-5-[(1*R*)-1,4-bis(benzoyloxy)-butyl]oxolan-2-yl}butyl Benzoate (7): Oil. IR: $\tilde{\nu}$ = 2956 (br. w), 2877 (br. w), 1716 (br. s), 1601 (w), 1584 (w), 1451 (w), 1314 (w), 1272 (br. s), 1176 (w), 1112 (m), 1069 (w), 1025 (w), 710 (m), cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 8.09 (d, J = 7.6 Hz, 4 H), 8.01 (d, J = 7.0 Hz, 4 H), 7.60–7.27 (m, 12 H), 5.49–5.24 (m, 2 H), 4.47–4.24 (br. s, 4 H), 4.24–4.04 (m, 2 H), 2.11–1.67 (m, 12 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 166.3, 166.1, 132.8, 132.7, 130.1, 130.0, 129.5, 129.4, 128.2, 128.1, 79.8, 75.0, 64.4, 27.7, 27.4, 24.7 ppm. HRMS (ESI): calcd. for $C_{40}H_{40}NaO_9$ [M + Na]$^+$ 687.2570; found 687.2566.

(±)-(*R*)-1-{(2*R*,5*S*)-5-[(*S*)-1-(Benzoyloxy)undecyl]tetrahydrofuran-2-yl}butane-1,4-diyl Dibenzoate (9): Oil. IR: $\tilde{\nu}$ = 2924 (m), 2852 (w), 1718 (s), 1271 (s), 1112 (m), 1069 (w), 1026 (w), 710 (m) cm^{-1}. ^1H NMR: (200 MHz, $CDCl_3$): δ = 8.18–7.91 (m, 6 H), 7.60–7.31 (m, 9 H), 5.42–5.14 (m, 2 H), 4.30 (t, J = 5.6 Hz, 2 H), 4.21–4.06 (m, 2 H), 2.07–1.51 (m, 12 H), 1.46–1.05 (m, 10 H), 0.84 (t, J = 6.8 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 166.5, 166.3, 132.9, 132.81, 132.80, 130.4, 130.2, 130.1, 129.8, 129.7, 129.5, 128.35, 128.30, 80.1, 79.8, 75.9, 75.2, 64.6, 31.9, 30.9, 29.55, 29.53, 29.50, 27.8, 27.5, 25.4, 24.9, 22.6, 14.1 ppm. HRMS (ESI): calcd. for $C_{40}H_{50}NaO_7$ [M + Na]$^+$ 665.3454; found 665.3458.

(±)-[(1*R*,4*R*,5*S*,7*R*)-4-(Benzoyloxy)-6-oxabicyclo[3.2.1]octan-7-yl]-methyl Benzoate (11): Oil. IR: $\tilde{\nu}$ = 2953 (br. w), 2874 (br. w), 1716 (s), 1450 (w), 1335 (w), 1313 (w), 1271 (s), 1176 (w), 1114 (w), 1098 (w), 1069 (w), 1026 (w), 941 (w), 711 (m) cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 8.13–8.02 (d, J = 7.3 Hz, 2 H), 7.63–7.35 (m, 6 H), 4.94 (dd, J = 9.2, 6.7 Hz, 1 H), 4.75–4.51 (m, 3 H), 4.40 (br. dd, J = 9.6, 6.1 Hz, 1 H), 2.40 (br. s, 1 H), 2.34–1.84 (m, 4 H), 1.78 (d, J = 11.8 Hz, 1 H), 1.73–1.53 (m, 1 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 166.5, 166.2, 133.0, 132.9, 130.3, 130.1, 129.9, 129.8, 128.3, 128.2, 80.3, 78.0, 75.0, 63.8, 37.1, 35.8, 25.3, 24.0 ppm. HRMS (ESI): calcd. for $C_{22}H_{22}NaO_5$ [M + Na]$^+$ 389.1365; found 389.1362.

(±)-[(2*S*,6*S*)-Tetrahydro-2*H*-pyran-2,6-diyl]bis(methylene) Dibenzoate (13): Oil. IR: $\tilde{\nu}$ = 2940 (br. w), 1717 (s), 1601 (w), 1584 (w), 1451 (w), 1315 (w), 1275 (s), 1118 (br. m), 1070 (w), 1026 (w), 710 (s) cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 7.98 (d, J = 7.1 Hz, 4 H), 7.52 (t, J = 7.4 Hz, 2 H), 7.33 (t, J = 7.6 Hz, 4 H), 4.58 (dd, J = 12.5, 9.0 Hz, 2 H), 4.35–4.18 (m, 4 H), 1.96–1.39 (m, 6 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 166.5, 132.8, 130.0, 129.6, 128.3, 69.6, 65.2, 26.3, 18.5 ppm. HRMS (ESI): calcd. for $C_{21}H_{22}NaO_5$ [M + Na]$^+$ 377.1365; found 377.1368.

(±)-2-{(2*S*,6*S*)-6-[(Benzoyloxy)methyl]oxan-2-yl}propan-2-yl Benzoate (15): Oil. IR: $\tilde{\nu}$ = 2867 (w), 2940 (br. w), 1720 (s), 1602 (w), 1583 (w), 1451 (m), 1386 (w), 1366 (w), 1314 (m), 1275 (br. s), 1113 (br. m), 1070 (w), 1026 (w), 710 (s) cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 8.00 (d, J = 8.1 Hz, 2 H), 7.95 (d, J = 8.1 Hz, 2 H), 7.57–7.46 (m, 2 H), 7.35 (td, J = 7.9, 3.3 Hz, 4 H), 4.81 (dd, J = 10.4, 7.8 Hz, 1 H), 4.45–4.30 (m, 2 H), 4.45–4.24 (m, 2 H), 4.07 (d, J = 10.8 Hz, 1 H), 1.97–1.36 (m, partly overlapping with methyl signals, 6 H), 1.59 (s, 3 H), 1.57 (s, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 166.4, 165.5, 132.9, 132.4, 131.8, 130.1, 129.6, 129.4, 128.3, 128.1, 84.0, 74.5, 71.0, 62.9, 25.5, 25.0, 22.9, 21.5, 19.0 ppm. HRMS (ESI): calcd. for $C_{23}H_{26}NaO_5$ [M + Na]$^+$ 405.1678; found 405.1676.

(±)-2-{(2*S*,6*R*)-6-[(Benzoyloxy)methyl]oxan-2-yl}propan-2-yl Benzoate (17): Oil. IR: $\tilde{\nu}$ = 2983 (w), 2942 (br. w), 2858 (w), 1716 (br. s), 1602 (w), 1583 (w), 1451 (m), 1384 (w), 1367 (w), 1314 (m), 1290 (s), 1274 (s), 1118 (m), 1069 (w), 1027 (w), 711 (s) cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 7.98 (m, 4 H), 7.58–7.45 (m, 2 H), 7.37 (t, J = 7.6 Hz, 4 H), 4.30 (app d, J = 5.3 Hz, 2 H), 3.91–3.71 (m, 2 H), 2.08–1.91 (m, 1 H), 1.62 (s, 3 H), 1.57 (s, 3 H), 1.80–1.21 (m, partly overlapping with methyl signals, 6 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 166.4, 165.5, 132.8, 132.4, 131.8, 130.2, 129.5, 129.4, 128.2, 128.1, 83.8, 81.4, 75.9, 67.6, 27.7, 24.9, 23.0, 21.6 ppm. HRMS (ESI): calcd. for $C_{23}H_{26}NaO_5$ [M + Na]$^+$ 405.1678; found 405.1677.

(±)-[(2*S*,6*S*)-4-(Benzoyloxy)-tetrahydro-2*H*-pyran-2,6-diyl]bis-(methylene) Dibenzoate (19): Oil. IR: $\tilde{\nu}$ = 2857 (br. w), 1720 (s), 1601 (w), 1583 (w), 1451 (m), 1315 (m), 1272 (br. s), 1176 (w), 1110 (br. m), 1026 (m), 710 (m) cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 8.13–7.94 (m, 6 H), 7.64–7.41 (m, 3 H), 7.34 (t, J = 7.6 Hz, 6 H), 5.57–5.40 (m, 1 H), 4.84 (dd, J = 11.5, 8.0 Hz, 1 H), 4.74–4.49 (m, 2 H), 4.50–4.21 (m, 3 H), 2.27 (dt, J = 13.7, 4.3 Hz, 1 H), 2.05 (t, J = 5.5 Hz, 2 H), 1.85 (dt, J = 13.8, 7.0 Hz, 1 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 166.3, 165.7, 133.2, 132.9, 129.9, 129.85, 129.80, 129.6, 129.5, 128.5, 128.3, 68.9, 67.6, 67.1, 65.3, 65.1, 31.6, 31.4 ppm. HRMS (ESI): calcd. for $C_{28}H_{26}NaO_7$ [M + Na]$^+$ 497.1576; found 497.1573.

(±)-[(2*S*,6*S*)-4-Benzoylmorpholine-2,6-diyl]bis(methylene) Dibenzoate (20): Oil. IR: $\tilde{\nu}$ = 2955 (br. w), 1721 (s), 1639 (br. s), 1602 (w), 1451 (m), 1273 (br. s), 1114 (m), 1070 (w), 1027 (w), 711 (s) cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 8.14–7.73 (br. m, 6 H), 7.53 (t,

J = 7.3 Hz, 3 H), 7.48–7.27 (m, 6 H), 4.76–4.43 (br. m, 2 H), 4.43–4.17 (br. m, 4 H), 4.17–3.75 (br. m, 2 H), 3.75–3.38 (br. m, 2 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 171.1, 166.0, 134.7, 133.1, 130.0, 129.6, 129.5, 128.6, 128.3, 127.0, 68.8, 62.8, 47.8, (br) 43.4 (br) ppm. HRMS (ESI): calcd. for $C_{27}H_{25}NNaO_6$ $[M + Na]^+$ 482.1580; found 482.1583.

(1*R*)-1-((2*R*,5*S*)-5-{(1*S*)-1-(Acetyloxy)-15-[(5*S*)-5-methyl-2-oxo-2,5-dihydrofuran-3-yl]pentadecyl}oxolan-2-yl)tridecyl Acetate (25): Oil. IR: $\tilde{\nu}$ = 2922 (br. s), 2852 (m), 1735 (br. s), 1459 (w), 1370 (w), 1318 (w), 1237 (s), 1073 (w), 1025 (m), 949 (w) cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 6.98 (br. q, J = 1.3 Hz, 1 H), 4.99 (br. q, J = 6.7 Hz, 1 H), 4.94–4.81 (m, 3 H), 4.01–3.89 (m, 2 H), 2.26 (t, J = 7.6 Hz, 2 H), 2.07 (s, 6 H), 2.01–1.16 (m, 48 H), 1.40 (d, J = 6.8 Hz, 3 H), 0.87 (t, J = 6.1 Hz, 5 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 173.8, 170.7, 148.8, 134.3, 79.8, 77.4, 75.4, 31.9, 30.8, 29.6, 29.6, 29.3, 29.3, 29.2, 27.8, 27.4, 25.3, 25.2, 22.7, 21.1, 19.2, 14.1 ppm. HRMS (ESI): calcd. for $C_{41}H_{72}NaO_7$ $[M + Na]^+$ 699.5176; found 699.5180.

(1*R*)-1-[(2*R*,5*S*)-5-[(1*S*)-1-(Benzoyloxy)-15-[(5*S*)-5-methyl-2-oxo-2,5-dihydrofuran-3-yl]pentadecyl]oxolan-2-yl]tridecyl Benzoate (26): Oil. IR: $\tilde{\nu}$ = 2917 (m), 2850 (w), 1716 (s), 1599 (w), 1585 (w), 1451 (m), 1361 (w), 1311 (w), 1272 (s), 1248 (m), 1121 (m), 1023 (w), 771 (w), 714 (m) cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.07 (d, J = 7.3 Hz, 4 H), 7.53 (t, J = 7.4 Hz, 2 H), 7.38 (t, J = 7.4 Hz, 4 H), 6.98 (s, 1 H), 5.23 (app q, J = 5.5 Hz, 2 H), 4.99 (br. q, J = 7.3 Hz, 1 H), 4.17–4.03 (m, 2 H), 2.26 (t, J = 7.9 Hz, 2 H), 2.05–1.09 (m, 48 H), 1.40 (d, J = 6.8 Hz, 3 H), 0.87 (t, J = 6.0 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 174.5, 166.3, 166.2, 148.8, 134.3, 132.7, 130.5, 129.7, 128.3, 79.9, 77.4, 76.0, 31.9, 30.8, 29.63, 29.56, 29.50, 29.3, 29.2, 27.9, 27.4, 25.5, 25.2, 22.7, 19.2, 14.1 ppm. HRMS (ESI): calcd. for $C_{51}H_{76}NaO_7$ $[M + Na]^+$ 823.5489; found 823.5491.

Procedure A for the Oxidative Cleavage of Tetrahydrofuran Substrates: PCC (2 mol-% from a 0.01 M stock solution in CH_3CN) was added to a suspension of H_5IO_6 (3.2 equiv.) in CH_3CN at room temp. with vigorous stirring. After 5 min, a solution of the THF compound (1 equiv.) in CH_3CN was added. The overall volume of CH_3CN was such that the final concentration of the solution was 0.05 M. After complete consumption of the starting material (TLC control, typically 30–40 min), EtOH (excess) was added, and stirring was continued until the colour of the solution turned from yellow to green (ca. 5 min). Then silica (excess) was added, and the solvent was evaporated under reduced pressure. The resulting powder was loaded onto a silica gel column. Flash chromatography, eluting with $CHCl_3$/MeOH (100:0 to 9:1), gave the desired product.

Procedure B for the Oxidative Cleavage of Tetrahydropyran Substrates: PCC (4 mol-% from a 0.01 M stock solution in CH_3CN) was added to a suspension of H_5IO_6 (4.0 equiv.) in CH_3CN at room temp. with vigorous stirring. After 5 min, a solution of the THP compound (1 equiv.) in CH_3CN was added. The overall volume of CH_3CN was such that the final concentration of the solution was 0.05 M. After complete consumption of the starting material (TLC control, typically 6–8 h), EtOH (excess) was added, and stirring was continued until the colour of the solution turned from yellow to green (ca. 5 min). Then silica (excess) was added, and the solvent was evaporated under reduced pressure. The resulting powder was loaded onto a silica gel column. Flash chromatography, eluting with chloroform/methanol (100:0 to 9:1), gave the desired product.

2,5-Dioxohexane-1,6-diyl Dibenzoate (2): Benzoate-protected tetrahydrofuran **1** (22.0 mg, 0.065 mmol) was subjected to Procedure A to give title compound **2** (22.3 mg, 0.063 mmol, 97%) as a colourless solid. m.p. 138–140 °C. IR (thin film): $\tilde{\nu}$ = 2949 (w), 1724 (s), 1600 (w), 1451 (w), 1408 (m), 1271 (s), 1128 (w), 1101 (w), 1063 (w), 1028 (w), 988 (w), 702 (m) cm^{-1}. ^{1}H NMR and ^{13}C NMR see ref.[6]

2,5-Dioxohexane-1,6-diyl Diacetate (4): Acetate-protected tetrahydrofuran **3** (24.5 mg, 0.113 mmol) was subjected to Procedure A to give title compound **4** (20.8 mg, 0.090 mmol, 80%) as a colourless solid. m.p. 86–88 °C. IR (thin film): $\tilde{\nu}$ = 3004 (w), 2934 (w), 1763 (s), 1722 (s), 1415 (s), 1367 (m), 1304 (w), 1281 (m), 1232 (br. s), 1102 (w), 1038 (br. m), 1034 (w), 960 (w), 841 (w), 755 (br. w), 713 (w), 682 (w), 619 (w) cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.69 (s, 4 H), 2.74 (s, 4 H), 2.15 (s, 6 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 202, 170.2, 67.9, 31.9, 20.4 ppm. HRMS (ESI): calcd. for $C_{10}H_{14}NaO_6$ $[M + Na]^+$ 253.0688; found 253.0691.

2,5-Dioxohexane-1,6-diyl Bis(4-methylbenzenesulfonate) (6): Tosylate-protected tetrahydrofuran **5** (15.7 mg, 0.036 mmol) was subjected to Procedure A to give title compound **6** (13.8 mg, 0.030 mmol, 85%) as an oil. IR (thin film): $\tilde{\nu}$ = 2922 (br. w), 2852 (w), 1732 (m), 1597 (w), 1359 (m), 1189 (m), 1176 (s), 1091 (w), 1003 (br. m), 814 (m), 667 (m) cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.81 (d, J = 8.3 Hz, 4 H), 7.37 (d, J = 8.1 Hz, 4 H), 4.52 (s, 4 H), 2.80 (s, 4 H), 2.46 (s, 6 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 201.7, 145.6, 132.1, 130.1, 128.1, 71.7, 32.2, 21.7 ppm. HRMS (ESI): calcd. for $C_{20}H_{22}NaO_8S_2$ $[M + Na]^+$ 477.0654; found 477.0658.

(±)-(4*R*,9*S*)-5,8-Dioxododecane-1,4,9,12-tetrayl Tetrabenzoate (8): Benzoate-protected tetrahydrofuran **7** (122.0 mg, 0.184 mmol) was subjected to Procedure A to give title compound **8** (92.3 mg, 0.136 mmol, 74%) as a white solid. m.p. 123–125 °C. IR (thin film): $\tilde{\nu}$ = 2960 (br. w), 2917 (w), 1716 (br. s), 1600 (w), 1584 (w), 1451 (w), 1315 (w), 1272 (br. s), 1112 (br. m), 1070 (w), 1026 (w), 710 (m) cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.06 (t, J = 8.3 Hz, 8 H), 7.82–7.26 (m, 12 H), 5.36 (t, J = 5.9 Hz, 2 H), 4.39 (t, J = 5.8 Hz, 4 H), 3.15–2.62 (m, 4 H), 2.33–2.07 (m, 2 H), 2.07–1.87 (m, 2 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 205.7, 166.5, 166.0, 133.5, 132.8, 130.1, 129.8, 129.5, 129.1, 128.5, 128.3, 78.3, 64.1, 31.8, 27.4, 24.5 ppm. HRMS (ESI): calcd. for $C_{40}H_{38}NaO_{10}$ $[M + Na]^+$ 701.2363; found 701.2367.

(±)-(4*R*,9*S*)-5,8-Dioxononadecane-1,4,9-triyl Tribenzoate (10): Benzoate-protected tetrahydrofuran **9** (11.6 mg, 0.018 mmol) was subjected to Procedure A to give title compound **10** (7.2 mg, 0.011 mmol, 61%) as an oil. IR (thin film): $\tilde{\nu}$ = 2923 (br. m), 2853 (w), 1717 (br. s), 1602 (w), 1451 (w), 1315 (w), 1271 (br. s), 1176 (w), 1112 (m), 1070 (w), 1026 (w), 711 (m) cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.08 (d, J = 7.6 Hz, 4 H), 8.03 (d, J = 7.7 Hz, 2 H), 7.59 (dd, J = 7.9, 5.9 Hz, 2 H), 7.54 (t, J = 7.4 Hz, 1 H), 7.46 (t, J = 7.7 Hz, 4 H), 7.42 (t, J = 7.7 Hz, 2 H), 5.35 (dd, J = 8.0, 4.5 Hz, 1 H), 5.25 (dd, J = 6.9, 5.9 Hz, 1 H), 4.43–4.34 (m, 2 H), 2.95 (dt, J = 14.9, 6.0 Hz, 2 H), 2.85–2.75 (m, 2 H), 2.23–2.08 (m, 2 H), 1.96 (dq, J = 13.4, 6.2 Hz, 4 H), 1.48 (s, 2 H), 1.28 (t, J = 23.1 Hz, 14 H), 0.87 (t, J = 6.9 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 206.2, 205.8, 166.5, 166.2, 166.1, 133.5, 133.4, 132.9, 130.1, 129.83, 129.81, 129.6, 129.4, 129.1, 128.54, 128.49, 128.34, 79.0, 78.4, 64.2, 31.87, 31.83, 30.8, 29.7, 29.53, 29.51, 29.35, 29.29, 29.21, 27.5, 25.3, 24.6, 22.7, 14.1 ppm. HRMS (ESI): calcd. for $C_{40}H_{48}NaO_8$ $[M + Na]^+$ 679.3247; found 679.3245.

(±)-2-[(1*S*,4*R*)-4-(Benzoyloxy)-3-oxocyclohexyl]-2-oxoethyl Benzoate (12): Benzoate-protected tetrahydrofuran **11** (17.7 mg, 0.048 mmol) was subjected to Procedure A to give title compound **12** (13.7 mg, 0.036 mmol, 75%) as white needles. m.p. 156–157 °C. IR (thin film): $\tilde{\nu}$ = 2934 (br. w), 1721 (br. s), 1601 (w), 1584 (w), 1451 (m), 1414 (w), 1316 (m), 1274 (br. s), 1177 (w), 1114 (m), 1065

(m), 1026 (w), 996 (w), 710 (m) cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 8.17–8.00 (m, 4 H), 7.75–7.34 (m, 6 H), 5.38 (dd, J = 8.9, 6.2 Hz, 1 H), 5.12 (d, J = 16.8 Hz, 1 H), 4.85 (d, J = 16.8 Hz, 1 H), 3.64–3.09 (m, 1 H), 2.85 (ddd, J = 14.5, 4.4, 1.5 Hz, 1 H), 2.58 (ddd, J = 14.5, 5.7, 0.6 Hz, 1 H), 2.49–2.09 (m, 4 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 204.0, 201.6, 165.9, 165.5, 133.6, 133.3, 130.0, 129.9, 129.4, 128.9, 128.5, 128.4, 75.7, 67.0, 45.4, 40.0, 28.9, 24.5 ppm. HRMS (ESI): calcd. for $C_{22}H_{20}NaO_6$ $[M + Na]^+$ 403.1158; found 403.1161. Single crystal X-ray diffraction data for **12** (Figure 1): $C_{22}H_{20}O_6$, M = 380.38, monoclinic, a = 5.300(5), b = 10.946(4), c = 32.574(9) Å, β = 97.37(3)°, V = 1874(2) $Å^3$, T = 298 K, space group $P2_1/c$, Z = 4, μ(Mo-K_α) = 0.098 mm^{-1}, 10511 reflections measured, 3248 unique [R(int) = 0.0690] which were used in all calculations. Final agreement indices were R = 0.0573 [$I > 2\sigma(I)$]. and $wR(F^2)$ = 0.1421 (all data).

2,6-Dioxoheptane-1,7-diyl Dibenzoate (14): Benzoate-protected tetrahydropyran **13** (24.1 mg, 0.068 mmol) was subjected to Procedure B to give title compound **14** (21.3 mg, 0.058 mmol, 85%) as a white solid. m.p. 123–125 °C. IR (thin film): $\tilde{\nu}$ = 2949 (br. w), 2918 (w), 2850 (w), 1724 (br. s), 1600 (w), 1451 (w), 1408 (m), 1271 (br. s), 1128 (w), 1101 (m), 1063 (m), 1028 (m), 988 (w), 702 (m) cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 8.09 (d, J = 7.0 Hz, 4 H), 7.60 (t, J = 7.3 Hz, 2 H), 7.46 (t, J = 7.4 Hz, 4 H), 4.87 (s, 4 H), 2.61 (t, J = 6.8 Hz, 4 H), 2.01 (quin, J = 6.8 Hz, 2 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 203.6, 165.9, 133.4, 129.9, 129.6, 128.5, 68.4, 37.2, 16.7 ppm. HRMS (ESI): calcd. for $C_{21}H_{20}NaO_6$ $[M + Na]^+$ 391.1158; found 391.1159.

7-Methyl-2,6-dioxooctane-1,7-diyl Dibenzoate (16): Benzoate-protected tetrahydropyrans **15** (26.4 mg, 0.068 mmol) and **17** (21.0 mg, 0.055 mmol) were subjected to Procedure B to give title compound **16** (25.7 mg, 0.065 mmol, 95% from **15**; 18.2 mg, 0.046 mmol, 83% from **17**) as an oil. IR (thin film): $\tilde{\nu}$ = 2990 (w), 2937 (br. w), 1721 (br. s), 1601 (w), 1584 (w), 1451 (m), 1416 (w), 1367 (w), 1316 (m), 1286 (br. s), 1113 (m), 1070 (m), 1026 (m), 712 (s) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 8.07 (d, J = 7.2 Hz, 2 H), 8.01 (d, J = 7.2 Hz, 2 H), 7.60–7.54 (m, 2 H), 7.45 (t, J = 7.4 Hz, 2 H), 7.43 (t, J = 7.4 Hz, 2 H), 4.88 (s, 2 H), 2.66–2.50 (q, 4 H), 1.97 (quin, J = 6.8 Hz, 2 H), 1.59 (s, 6 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 208.4, 203.8, 165.8, 133.3, 129.9, 129.8, 129.2, 128.4, 84.1, 68.4, 37.2, 33.8, 23.7, 16.9 ppm. HRMS (ESI): calcd. for $C_{23}H_{24}NaO_6$ $[M + Na]^+$ 419.1471; found 419.1473.

2,6-Dioxoheptane-1,4,7-triyl Tribenzoate (19): Benzoate-protected tetrahydropyran **18** (27.0 mg, 0.057 mmol) was subjected to Procedure B to give title compound **19** (21.5 mg, 0.044 mmol, 78%) as a white solid. m.p. 148–150 °C. IR (thin film): $\tilde{\nu}$ = 3068 (w), 2929 (w), 1720 (s), 1601 (w), 1583 (w), 1451 (w), 1406 (br. w), 1314 (w), 1275 (s), 1177 (w), 1112 (w), 1069 (w), 1026 (w), 711 (m) cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 8.18–7.91 (m, 6 H), 7.67–7.52 (m, 3 H), 7.50–7.34 (m, 6 H), 5.86 (quin, J = 6.0 Hz, 1 H), 4.96 (d, J = 16.9 Hz, A part of an AB system, 2 H), 4.87 (d, J = 16.9 Hz, B part of an AB system, 2 H), 3.23–2.97 (m, 4 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 201.0, 165.8, 165.6, 133.5, 133.3, 129.9, 129.7, 129.6, 129.0, 128.5, 68.7, 66.5, 41.9 ppm. HRMS (ESI): calcd. for $C_{28}H_{24}NaO_8$ $[M + Na]^+$ 511.1369; found 511.1366.

3,3′-Benzamidobis(2-oxopropane-3,1-diyl) Dibenzoate (21): Benzoate-protected morpholine **20** (20.0 mg, 0.044 mmol) was subjected to Procedure B. The reaction mixture was filtered and evaporated to dryness, and the crude material was separated by HPLC (hexane/EtOAc, 6:4) to give title compound **21** (5.2 mg, 0.011 mmol, 26%), and compounds **22** (3.9 mg, 0.008 mmol, 18%) and **23** (2.3 mg, 0.005 mmol, 12%). Data for **21**: Oil. IR (thin film): $\tilde{\nu}$ = 2921 (w), 2848 (w), 1725 (br. s), 1644 (m), 1601 (w), 1451 (m), 1414 (w), 1315 (w), 1275 (s), 1112 (m), 1069 (m), 1027 (w), 712 (m) cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 8.10 (d, J = 7.6 Hz, 2 H), 7.99 (d, J = 7.7 Hz, 2 H), 7.60 (t, J = 7.3 Hz, 2 H), 7.54–7.31 (m, 9 H), 5.04 (s, 2 H), 4.74 (s, 2 H), 4.52 (s, 2 H), 4.42 (s, 2 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 200.0, 199.8, 172.3, 166.0, 165.7, 134.2, 133.7, 133.6, 130.5, 129.94, 129.87, 128.80, 128.5, 126.8, 67.5, 67.0, 56.8, 52.6 ppm. HRMS (ESI): calcd. for $C_{27}H_{23}NNaO_7$ $[M + Na]^+$ 496.1372; found 496.1373.

1-(Benzoyloxy)-3-(*N*-formyl-1-phenylformamido)propan-2-yl 2-(Benzoyloxy)acetate (22): Oil. IR (thin film): $\tilde{\nu}$ = 2949 (br. w), 2926 (br. w), 2849 (w), 1762 (w), 1727 (s), 1673 (s), 1602 (w), 1451 (w), 1275 (br. s), 1206 (br. m), 1117 (br. m), 1071 (w) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.96 (s, 1 H), 8.06 (d, J = 7.7 Hz, 2 H), 8.03 (d, J = 8.4 Hz, 2 H), 7.62–7.53 (m, J = 8.1 Hz, 5 H), 7.51–7.39 (m, 6 H), 5.72 (d, J = 3.4 Hz, 1 H), 4.85 (d, J = 16.0 Hz, A part of an AB system, 1 H), 4.79 (d, J = 16.0 Hz, B part of an AB system, 1 H), 4.60 (dd, J = 12.2, 3.8 Hz, 1 H), 4.54–4.43 (m, 3 H), 4.15 (dd, J = 14.0, 2.9 Hz, 1 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 172.1, 167.7, 166.0, 165.8, 164.2, 133.4, 133.3, 133.0, 132.3, 129.9, 129.8, 129.4, 129.3, 129.0, 128.9, 128.5, 128.4, 70. 6, 63.6, 61.1, 40.5 ppm. HRMS (ESI): calcd. for $C_{27}H_{23}NNaO_8$ $[M + Na]^+$ 512.1321; found 512.1320.

1-(Benzoyloxy)-3-(phenylformamido)propan-2-yl 2-(Benzoyloxy)-acetate (23): Oil. IR (thin film): $\tilde{\nu}$ = 3380 (br. w), 3300 (br. w), 3061 (w), 2934 (w), 1726 (s), 1645 (w), 1537 (br. w), 1451 (w), 1275 (s), 1203 (w), 1117 (m), 709 (m) cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 8.06–7.95 (m, 4 H), 7.83 (d, J = 7.9 Hz, 2 H), 7.65–7.35 (m, 9 H), 6.75 (br. t, J = 5.4 Hz, 1 H), 5.59–5.42 (m, J = 7.3 Hz, 1 H), 4.92 (d, J = 15.8 Hz, A part of an AB system, 1 H), 4.82 (d, J = 15.8 Hz, B part of an AB system, 1 H), 4.60 (dd, J = 12.2, 4.1 Hz, 1 H), 4.49 (dd, J = 12.2, 5.5 Hz, 1 H), 3.99 (ddd, J = 14.5, 6.5, 3.9 Hz, 1 H), 3.67 (ddd, J = 14.5, 7.2, 5.6 Hz, 1 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 167.7, 167.4, 166.7, 166.2, 133.8, 133.7, 133.3, 131.6, 129. 9, 129.7, 129.6, 129.3, 128.555, 128.548, 128.5, 127.1, 126.6, 72.2, 63.3, 61.7, 40.1 ppm. HRMS (ESI): calcd. for $C_{26}H_{23}NNaO_7$ $[M + Na]^+$ 484.4531; found 484.4520.

(13*R*,18*S*)-18-(Acetyloxy)-32-[(5*S*)-5-methyl-2-oxo-2,5-dihydrofuran-3-yl]-14,17-dioxodotriacontan-13-yl Acetate (27): *cis*-Reticulatacin diacetate **25** (5.4 mg, 0.008 mmol) was subjected to Procedure B. After being stirred for 12 h, the reaction mixture was filtered and evaporated to dryness, and the crude mixture was separated by HPLC (hexane/EtOAc, 8:2) to give title compound **27** (1.4 mg, 0.002 mmol, 30%) as a colourless oil. IR (thin film): $\tilde{\nu}$ = 2924 (s), 2853 (m), 1747 (br. s), 1374 (w), 1235 (br. m) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.99 (s, 1 H), 5.04–4.92 (m, 3 H), 2.88–2.75 (m, 2 H), 2.75–2.62 (m, 2 H), 2.26 (t, J = 7.6 Hz, 2 H), 2.14 (s, 6 H), 1.90–1.65 (m, 6 H), 1.66–1.17 (m, 38 H), 1.40 (d, J = 6.8 Hz, 3 H), 0.88 (t, J = 6.7 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 206.1, 173.9, 170.7, 148.8, 134.3, 78.6, 77.4, 31.9, 31.7, 30.5, 29.6, 29.5, 29.4, 29.2, 27.4, 25.21, 25.20, 22.7, 20.7, 19.2, 14.1 ppm. HRMS (ESI): calcd. for $C_{41}H_{70}NaO_8$ $[M + Na]^+$ 713.4968; found 713.4966.

(13*R*,18*S*)-18-(Benzoyloxy)-32-[(5*S*)-5-methyl-2-oxo-2,5-dihydrofuran-3-yl]-14,17-dioxodotriacontan-13-yl Benzoate (28): *cis*-Reticulatacin dibenzoate **26** (3.6 mg, 0.004 mmol) was subjected to Procedure B. After being stirred for 8 h, the reaction mixture was filtered and taken to dryness, and the crude mixture was separated by HPLC (hexane/EtOAc, 85:15) to give title compound **28** (1.6 mg, 0.002 mmol, 40%) as a colourless oil. $[\alpha]_D^{30}$ = –23.3 (c = 0.03, $CHCl_3$). IR (thin film): $\tilde{\nu}$ = 2924 (s), 2853 (m), 1756 (m), 1720 (s),

1453 (w), 1316 (w), 1271 (m), 1112 (br. w), 1028 (w), 712 (m) cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 8.08 (d, J = 7.1 Hz, 4 H), 7.60 (t, J = 7.3 Hz, 2 H), 7.46 (t, J = 7.4 Hz, 4 H), 6.98 (br. q, J = 1.7 Hz, 1 H), 5.24 (t, J = 6.4 Hz, 2 H), 4.99 (br. q, J = 6.8 Hz, 1 H), 3.05–2.67 (m, 4 H), 2.26 (t, J = 7.6 Hz, 2 H), 1.94 (app q, J = 6.5 Hz, 4 H), 1.64–1.15 (m, 40 H), 1.40 (d, J = 6.8 Hz, 3 H), 0.87 (t, J = 6.4 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 206.2, 173.9, 166.9, 166.2, 148.9, 134.3, 133.4, 129.8, 129.3, 128.5, 79.0, 77.4, 31.9, 31.8, 30.7, 29.7, 29.6, 29.5, 29.3, 29.2, 27.4, 25.3, 25.1, 22.7, 19.2, 14.1 ppm. HRMS (ESI): calcd. for $C_{51}H_{74}NaO_8$ $[M + Na]^+$ 837.5281; found 837.5284.

2-[6-(Hydroxymethyl)pyridin-2-yl]propan-2-ol (29b): NH_4OAc (4.0 mg, 0.052 mmol) and AcOH (3 μL) were added to a solution of diketone **16** (12.0 mg, 0.030 mmol) in dry MeOH (300 μL). After being stirred for 24 h at room temp. and 48 h at 55 °C, the reaction mixture was diluted with EtOAc (2 mL) and washed with $NaHCO_3$ (sat. aq.) and water. The organic phase was dried, filtered and concentrated under reduced pressure. Separation by preparative TLC (hexane/EtOAc, 3:7) gave **29a** (6.3 mg, 55%) and **30** (2.1 mg, 25%) as colourless oils. Data for **29a**: oil. IR (thin film): $\tilde{\nu}$ = 2923 (br. w), 2849 (w), 1716 (s), 1594 (w), 1450 (w), 1314 (w), 1265 (br. s), 1151 (w), 1108 (s), 1070 (w), 1026 (w), 709 (s) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 8.11 (d, J = 7.2 Hz, 2 H), 8.06 (d, J = 7.2 Hz, 2 H), 7.71 (t, J = 7.8 Hz, 1 H), 7.60–7.54 (m, 2 H), 7.48–7.42 (m, 4 H), 7.39 (d, J = 8.0 Hz, 1 H), 7.32 (d, J = 7.6 Hz, 1 H), 5.52 (s, 2 H), 1.94 (s, 6 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 166.3, 165.3, 155.3 154.9, 137.2, 133.1, 132.7, 129.7, 129.6, 128.4, 128.3, 119.3, 117.9, 83.3, 67.2, 27.6 ppm. HRMS (ESI): calcd. for $C_{23}H_{21}NNaO_4$ $[M + Na]^+$ 398.1368; found 398.1367.

K_2CO_3 (1.0 mg, 10 mol-%) was added to a solution of **30** (2.1 mg, 0.008 mmol) in MeOH. After being stirred for 30 min at room temp., AcOH was added until neutrality was reached, and then the mixture was evaporated under reduced pressure. The residue was redissolved in $CHCl_3$ and filtered to give pyridine diol **29b** (1.2 mg, 0.007 mmol, 85%) as an oil. Data for **29b**: IR (thin film): $\tilde{\nu}$ = 3420 (br. m), 2920 (br. m), 2853 (m), 1736 (br. m), 1462 (br. w), 1376 (br. w), 1260 (br. w), 1169 (br. w), 1099 (br. w), 1022 (br. w), 802 (w) cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 7.72 (t, J = 7.7 Hz, 1 H), 7.32 (d, J = 7.8 Hz, 1 H), 7.19 (d, J = 7.8 Hz, 1 H), 4.79 (s, 2 H), 1.57 (s, 6 H) ppm. HRMS (ESI): calcd. for $C_9H_{13}NNaO_2$ $[M + Na]^+$ 190.0844; found 190.0842.

[6-(Hydroxymethyl)pyridin-2-yl]methanol (31b): $NH_2OH{\cdot}HCl$ (5.8 mg, 0.084 mmol) was added to a solution of diketone **14** (9.4 mg, 0.024 mmol) in dry EtOH (1 mL). After being stirred for 16 h at room temp. and 8 h at reflux, $NaHCO_3$ (sat. aq.) was added until neutrality was reached, and then the mixture was concentrated under reduced pressure and filtered through a short pad of silica gel ($CHCl_3$/MeOH, 8:2). Purification by preparative TLC (hexane/EtOAc, 3:7) gave **31a** (5.4 mg, 0.016 mmol, 65%) as a colourless oil. Data for **31a**: IR (thin film): $\tilde{\nu}$ = 2917 (br. m), 2850 (m), 1716 (m), 1600 (w), 1585 (w), 1451 (w), 1361 (w), 1311 (w), 1272 (s), 1248 (m), 1173 (w), 1121 (m), 1023 (w), 771 (w), 714 (m) cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 8.16–8.08 (m, 4 H), 7.76 (t, J = 7.7 Hz, 1 H), 7.65–7.54 (m, 2 H), 7.52–7.43 (m 4 H), 7.41 (d, J = 7.2 Hz, 2 H), 5.51 (s, 4 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 166.2, 155.9, 137.6, 132.2, 129.8, 128.6, 128.5, 120.7, 67.0 ppm. HRMS (ESI): calcd. for $C_{21}H_{17}NNaO_4$ $[M + Na]^+$ 370.1055; found 370.1053.

Debenzoylation of **31a** (4.5 mg, 0.013 mmol) with K_2CO_3 in MeOH as described for **30** gave pyridine-2,6-diyldimethanol **31b** (1.5 mg, 0.011 mmol, 82%) as an oil. Spectroscopic data for **31b** were consistent with those previously reported for this compound.[33]

2,6-Bis(hydroxymethyl)-1λ^4-pyridin-1-olate (32b): $NH_2OH{\cdot}HCl$ (5.1 mg, 0.0073 mmol) was added to a solution of diketone **19** (10.5 mg, 0.021 mmol) in dry EtOH (500 μL). After being stirred for 32 h at room temp. and 15 h at reflux, $NaHCO_3$ (sat. aq.) was added until neutrality was reached, and then the mixture was concentrated under reduced pressure and filtered through a short pad of silica gel ($CHCl_3$/MeOH, 8:2). Purification by preparative TLC (hexane/EtOAc, 1:1) gave **32a** (5.3 mg, 0.014 mmol, 68%) as a colourless oil. Data for **32a**: IR (thin film): $\tilde{\nu}$ = 2924 (br. m), 2852 (w), 1717 (s), 1601 (w), 1449 (w), 1368 (w), 1264 (s), 1174 (m), 1115 (s), 1071 (m), 1027 (w), 845 (m), 769 (w), 709 (s) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 8.15 (d, J = 7.5 Hz, 4 H), 7.62 (t, J = 7.2 Hz, 2 H), 7.50 (t, J = 7.7 Hz, 4 H), 7.46 (d, J = 7.6 Hz, 2 H), 7.34 (t, J = 8.0 Hz, 1 H), 5.71 (s, J = 32.9 Hz, 4 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.7, 147.3, 133.5, 129.8, 129.3, 128.6, 125.5, 122.2, 60.8 ppm. HRMS (ESI): calcd. for $C_{21}H_{17}NNaO_5$ $[M + Na]^+$ 386.1010; found 370.1012.

Debenzoylation of **32a** (3.8 mg, 0.010 mmol) with K_2CO_3 in MeOH as described for **30** gave diol **32b** (1.2 mg, 0.008 mmol, 78%) as an oil. Data for **32b**: IR (thin film): $\tilde{\nu}$ = 3418 (br. m), 2918 (w), 2849 (w), 1644 (br. m), 1416 (w), 1358 (w), 1212 (w), 1166 (w), 1085 (w), 1031 (w) cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 7.36 (br. s, 3 H), 4.84 (br. s, 4 H) ppm. ^{13}C NMR (175 MHz, CD_3OD): δ = 157.6, 130.1, 122.4, 59.7 ppm. HRMS (ESI): calcd. for $C_7H_9NNaO_3$ $[M + Na]^+$ 178.0480; found 178.0481.

Converson of 31b to 32b: MCPBA (1.2 equiv., 0.030 mmol, 500 μL) from a stock solution (0.060 M) in $CHCl_3$ was added to a solution of pyridine diol **31b** (3.5 mg, 0.025 mmol) in $CHCl_3$ (500 μL). The mixture was stirred for 90 min at room temp. and then it was concentrated under reduced pressure. Separation by preparative TLC ($CHCl_3$/MeOH, 8:2) gave **32b** (1.4 mg, 0.009 mmol, 36%) as a colourless oil.

[6-(Hydroxymethyl)pyrazin-2-yl]methanol (33b): $NH_2OH{\cdot}HCl$ (4.8 mg, 0.069 mmol) was added to a solution of diketone **21** (10.8 mg, 0.023 mmol) in dry EtOH (500 μL). After being stirred for 6 h at room temp., $NaHCO_3$ (sat. aq.) was added until neutrality was reached, and then the mixture was concentrated under reduced pressure and filtered through a short pad of silica gel ($CHCl_3$/MeOH, 8:2). Purification by HPLC (hexane/EtOAc, 6:4) gave **33a** (5.6 mg, 0.016 mmol, 68%) as a colourless oil. Data for **33a**: IR: $\tilde{\nu}$ = 2917 (m), 2849 (w), 1719 (s), 1601 (w), 1451 (w), 1315 (w), 1266 (s), 1176 (w), 1110 (m), 1071 (w), 1025 (w), 709 (s) cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 8.74 (s, 2 H), 8.11 (d, J = 7.0 Hz, 4 H), 7.61 (t, J = 7.3 Hz, 2 H), 7.47 (t, J = 7.3 Hz, 4 H), 5.54 (s, 4 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 166.1, 150.9, 142.6, 133.5, 129.8, 129.4, 128.6, 65.1 ppm. HRMS (ESI): calcd. for $C_{20}H_{16}N_2NaO_4$ $[M + Na]^+$ 371.3418; found 371.3419.

Debenzoylation of **33a** (6.5 mg, 0.019 mmol) with K_2CO_3 in MeOH as described for **30** gave diol **33b** (1.7 mg, 0.012 mmol, 66%) as an oil. Data for **33b**: IR (thin film): $\tilde{\nu}$ = 3364 (br. m), 2924 (s), 2854 (m), 1723 (br. m), 1641 (br. m), 1576 (w), 1539 (w), 1490 (w), 1456 (w), 1418 (br. w), 1275 (br. m), 1160 (br. w), 1083 (br. m), 1022 (w), 713 (m) cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 8.58 (br. s, 2 H), 4.86 (br. s, 4 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 153.6, 141.5, 62.9 ppm. HRMS (ESI): calcd. for $C_6H_8N_2NaO_2$ $[M + Na]^+$ 163.0483; found 163.0485.

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

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