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Diastereoselective trimolecular condensation between indole, Meldrum's acid and chiral sugar-derived aldehydes

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This paper is dedicated to the memory of Professor Lajos Szabo (Technical University of Budapest, Hungary) who passed away on 20th December 2008, at the age of 81

ABSTRACT

The trimolecular condensation of indole, Meldrum's acid and chiral, sugar-derived aldehydes took place in good yield and high diastereoselectivity. The absolute configuration of the α-carbon of the chiral aldehydes ensured a predictable diastereocontrol of the newly created stereogenic centre except for (3a*R*,5*S*,6*S*,6a*R*)-6-benzyloxy-2,2-dimethyl-tetrahydrofuro[3,2-*d*][1,3]dioxole-5-carbaldehyde **3i**. In this case, the opposite stereochemistry may be explained by a less congested conformer of the Knoevenagel-adduct intermediate.

1. Introduction

Multicomponent reactions (MCRs) are one-pot reactions in which at least three partners are combined in a single reaction vessel to form new products incorporating a substantial part of the reacting partners. Rapidity, diversity, efficiency and environmental amiability are the key features of this widely used method.[1] Over the past decades multicomponent reactions have undoubtedly become a versatile tool for the construction of highly functionalised building blocks in the total synthesis of natural products[2] and in diversity-oriented synthesis of heterocyclic scaffolds for drug discovery.[3]

The expanding claim for chiral, polyfunctionalised molecules of biological interest triggered the development of enantio(diastereo)selective multicomponent processes[4] by using chiral starting materials, chiral catalysts[5] or very recently, organocatalysts.[6] Despite spectacular progress, such a multicomponent approach providing drug-like carbo- or heterocyclic scaffolds by a diastereoselective manner remains a challenge in synthetic organic and medicinal chemistry.

Some years ago we developed a trimolecular condensation between indole **1**, Meldrum's acid **2** and aldehydes for the preparation of conformationally constrained β-substituted tryptophans.[7] By extension of this method to chiral aldehydes such as D- or L-glyceraldehyde **3a** or Garner's aldehyde **3b** we have worked out a highly diastereoselective synthesis of chiral 3,4-furanone-, pyrrolidinone- or pyranone-annulated tetrahydro-β-carbolines (Fig. 1).[8]

In order to investigate the scope and limitation of this asymmetric multicomponent reaction we envisioned a study of the remote substituent effect on the diastereoselectivity by using several polyfunctional sugar-derived chiral aldehydes (Scheme 1). In addition, such an experience would facilitate the synthetic applications that can be carried out on the condensation products.

2. Results and discussion

According to our previous studies trimolecular condensation with D-glyceraldehyde **3c** afforded **4c** with (*S*) absolute configuration and high diastereoselectivity.[8]

In this regard, we first examined the substitution effect of the β-carbon by selecting functionalised chiral aldehydes bearing a dioxolane ring **3d** or bulky dithioacetal group **3e** (Scheme 1, Table 1). Chiral aldehyde **3d**, prepared from the corresponding dithioacetal[9] by periodic acid-mediated demercaptalation[10] was reacted crude with indole **1** and Meldrum's acid **2** under the classical conditions. We were delighted to find that the condensation product could be obtained as a diastereomeric mixture (95:5) from which the major isomer **4d** was isolated by crystallisation (Table 1, entry 2). The stereochemistry of the newly created stereogenic centre was determined by the conversion of **4d** to the corresponding lactone-ester **5d**. Thus, treatment of **4d** with HCl in methanol led to **5d** in 95% yield. The observed large coupling constant ($J_{H\text{-}3\text{–}H\text{-}4}$ = 13.1 Hz) together with a NOE cross-peak between H-4 and H-5 evidenced *trans* H-3/H-4 and *cis* H-4/H-5 relative configurations. Consequently, the absolute configuration of the newly created carbon in **4d** is (*S*).

When a freshly prepared dithioacetal group substituted aldehyde **3e**[11] was reacted with indole **1** and Meldrum's acid **2**, the corresponding condensation product **4e** was isolated in 71% yield with 92% de (Table 1, entry 3). Similarly, enantiomerically pure conden-

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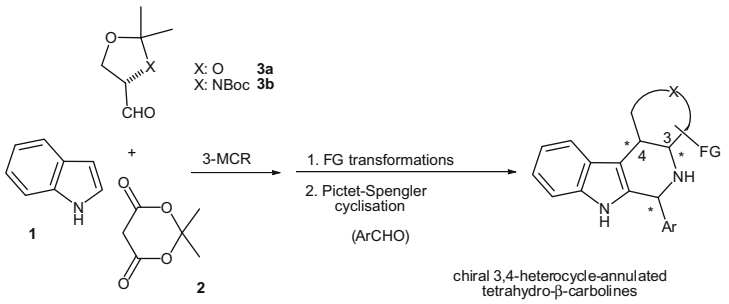
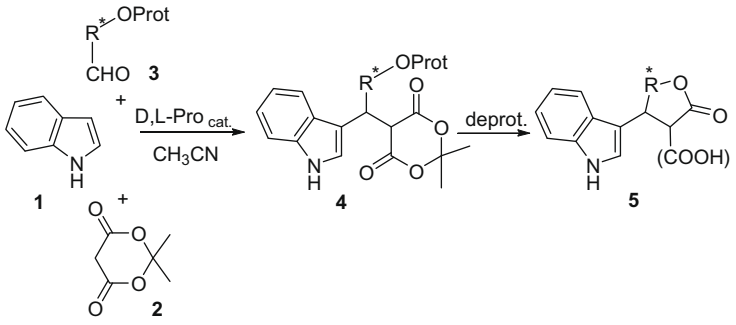


Figure 1.



Scheme 1.

sation product **4e** was obtained by crystallisation. The (*S*) configuration of the new stereogenic centre in **4e** was deduced from NMR data (couplings and NOE experiences) of lactone-acid **5e** obtained in 75% yield by aqueous HCl-assisted cleavage followed by ring closure.

By replacing the dioxolane protection of α-and β-hydroxyl functions by a benzyl protecting group we intended to examine the impact of conformationally mobile aldehydes on diastereoselectivity. Freshly prepared[12] dibenzyloxy-substituted aldehyde **3f** afforded condensation product **4f** in 67% yield with 96% de (Table 1, entry 4). Debenzylation of **4f** quantitatively provided lactone-acid **5f** of *trans* and *cis* relative configuration for H-3/H-4 and H-4/H-5 hydrogens, respectively. The absolute configuration of the newly created stereogenic centre in **4f** was again (*S*).

With these results in hand, we were keen to investigate whether a sterically congested group in the α- or β-position would influence the stereochemistry.

Orthogonally protected aldehydes bearing bulky *tert*-butyldimethylsilyloxy functions in α- or β-positions were prepared as depicted in Scheme 2. In both cases the other hydroxyl group was benzylated. Dihydroxythioacetal **6** after deprotonation was submitted to subsequent *O*-silylation and *O*-benzylation giving rise to an inseparable mixture of major **7** and minor **8** *O*-diprotected thioacetals (77/23). Periodic acid-mediated deprotection of this latter **7**/**8** afforded the corresponding mixture of aldehydes **3g**/**3h**[13] that was reacted without purification with indole **1** and Meldrum's acid **2** (Table 1, entry 5). The three-component condensation led to a mixture of four derivatives (total yield: 67%) from which the major diastereomer **4g** bearing a *tert*-butyldimethylsilyloxy group on the β-carbon was isolated in 48% yield by crystallisation. Since ^{1}H NMR couplings did not allow the determination of the stereochemistry of newly formed stereocenter, trimolecular condensation product **4g** was submitted to catalytic hydrogenation. Debenzylation of **4g** followed by spontaneous ring closure led to lactone-acid **5g** in quantitative yield. NOESY experiments of **5g** revealed correlations on the one hand between H-4 and H-5 protons and on the other hand between H-3 and indole H-2 protons corresponding to H-4/H-5 *cis* and H-3/H-4 *trans* relative configurations.

Minor diastereomer *epi*-**4g** obtained in 3% yield with the same aldehyde **3g** was isolated by preparative thin-layer chromatography. The diastereomeric ratio of trimolecular condensation products **4g**/*epi*-**4g** was 94 is to 6. Regioisomeric three-component condensation products **4h**/*epi*-**4h** obtained from **3h** were unexploited due to the complexity of the mixture.

At this point it was clear that the diastereoselectivity of the three-component reaction was noteworthy (de >90%) and that the (*S*)-absolute configuration was obtained independently from the substitution pattern (cyclic or non-cyclic) of α,β-dihydroxy chiral aldehydes. These highly efficient reactions require some mechanistic considerations. Three-component reactions have probably passed through an alkylidene Meldrum's acid intermediate **9**, formed by a proline-catalysed condensation.[14] Subsequent nucleophilic attack of indole **1** on the electron-deficient Michael acceptor intermediate **9** affords the corresponding condensation products **4**. The observed high *syn*-diastereoselectivity may be explained by the approach of indole from the γ-oxygen face on the reactive conformation wherein non-bonding 1,3-allyl-strain is minimized (Scheme 3).

Then it was interesting to investigate the substituent effect using bicylic *O*-benzyl protected aldehyde **3i**[15] prepared from 1,2,5,6-diisopropylidene-D-glucose according to a recently modified procedure.[16] The resulting crude aldehyde **3i** was directly reacted with indole **1**, Meldrum's acid **2** in the presence of a catalytic amount of D,L-proline to give three-component condensation product **4i** with high diastereoselectivity (de >95%) (Table 1, entry 6). Debenzylation of **4i** provoked a facile intramolecular cyclisation followed by elimination. A mixture of lactone-acid **5i** and its decarboxylated counterpart **5j** was isolated in 93% and 6% yield, respectively. The *trans* relative configuration between the indole ring and carboxylic acid function in **5i** was suggested by a large coupling constant $J_{H\text{-}6\text{–}H\text{-}7}$ = 12.3 Hz) of a doublet (H-6) at

Table 1
Synthesis of three-component products **4** from chiral aldehydes **3**, indole **1** and Meldrum's acid **2** and their transformation to lactones **5** according to Scheme 1

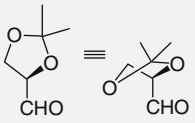
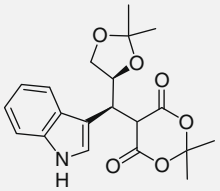
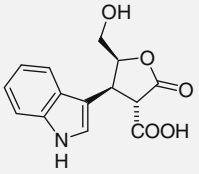
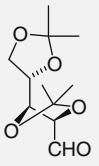
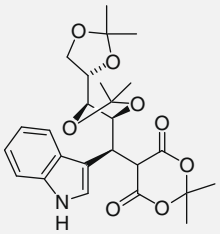
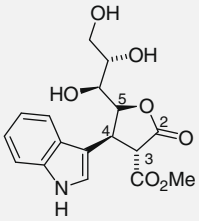
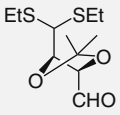
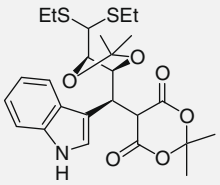
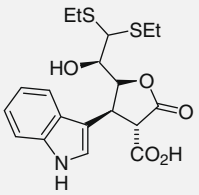
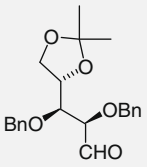
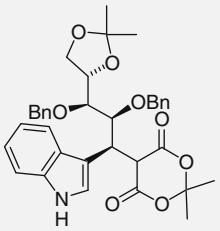
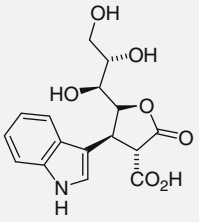
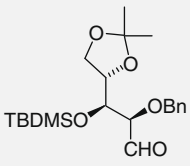
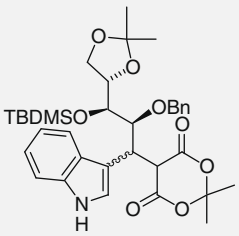
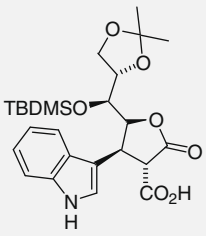
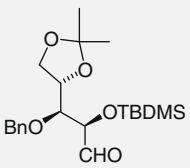
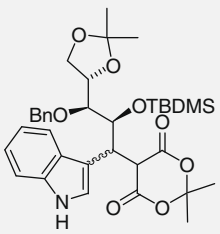
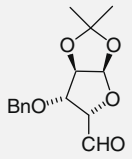
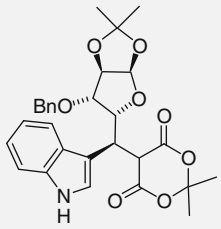
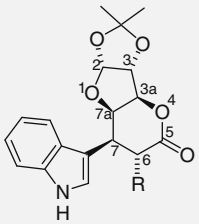
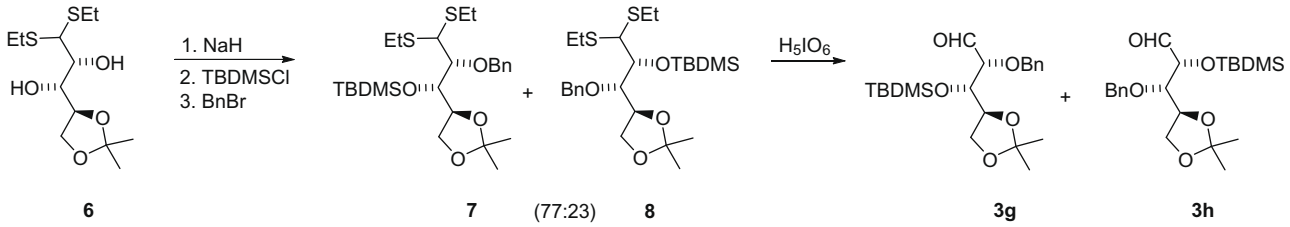
Entry	Aldehydes **3**[a]	Three-component products **4**[b]	Deprotection	Lactones **5**
1	 **3c**	 **4c** (76%, d.e. 92%)[8]	$HCl–H_2O$, THF 25 °C, 0.5 h	 **5c** (92%)[8]
2	 **3d**	 **4d** (55%, d.e. 90%)	HCl–MeOH 25 °C, 0.5 h	 **5d** (95%)
3	 **3e**	 **4e** (71%, d.e. 92%)	$HCl–H_2O$, THF 25 °C, 48 h	 **5e** (75%)
4	 **3f**	 **4f** (67%, d.e. 96%)	H_2-PdC, AcOEt 25 °C, 24 h	 **5f** (95%)
5	 **3g**	 **4g**/***epi*-4g** (48% / 3%, d.e. 88%)	H_2-PdC, AcOEt 25 °C, 24 h	 **5g** (from **4g**) (98%)
	 **3h**	 **4h**/***epi*-4h** (15%)		
	3g/**3h** : 77/23			

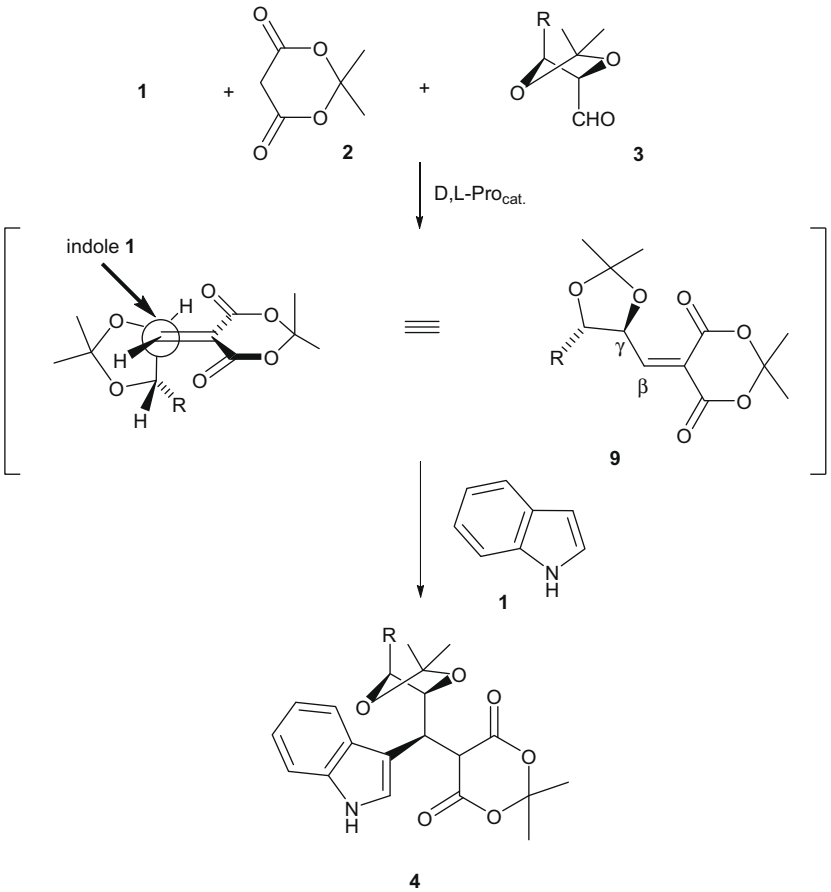
Table 1 (*continued*)

Entry	Aldehydes **3**[a]	Three-component products **4**[b]	Deprotection	Lactones **5**
6	 **3i**	 **4i** (81%, d.e. 95%)	H_2-PdC, AcOEt 25 °C, 24 h	 **5i** R = COOH (93%) **5j** R = H (6%)

[a] Aldehydes were used without further purification.
[b] Diastereomeric excess was determined by ^{1}H NMR after column chromatography purification.



Scheme 2.



Scheme 3.

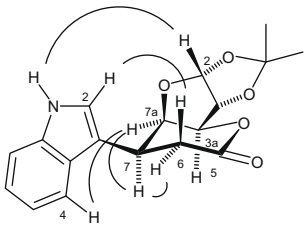


Figure 2.

δ = 4.25 ppm. The small coupling ($J_{H\text{-}7\text{–}H\text{-}7a}$ = 3.6 Hz) of the doublet of doublet attributed to H-7 was in accord with a *cis* relative configuration between H-7 and H-7a.

Further support for the stereochemistry of this functionalised tetrahydrofuro[3,2-*b*]tetrahydropyranone appendage was furnished by exhaustive NOESY experiments made on the more stable decarboxylated lactone **5j** (Fig. 2). Thus, cross-peaks were identified on the one side between H-7 and H-6a, H-7a and H-4 of the indole ring, and on the other side between H-6b and H-2 of the indole moiety and H-2 and indole NH. All these spectroscopic data supported the (*S*) absolute configuration for the C-7 carbon. This configuration is the opposite to that of what we observed when L-glyceraldehyde **3a** was reacted with indole **1** and Meldrum's acid **2**.[8]

The highly *anti*-selective three-component condensation occurred with *O*-benzyl substituted aldehyde **3i** and was contrary to the results of Sabitha et al. using hydroxyl or methoxy-group substituted analogs.[17] The opposite absolute configuration observed in our case may result from a more stable conformer of Knoevenagel product **9i** which is free of steric repulsion between *O*-benzyl group and the carbonyl function of Meldrum's acid appendage (Scheme 4). The intermediacy of such alkylidene Meldrum's acid in our three-component condensation was supported by reacting **9i**[18] with indole **1**, as depicted in Scheme 4. The condensation was completely diastereoselective and we isolated the same three-component product **4i** that was obtained under classical conditions.

3. Conclusion

In conclusion, we found that the three-component reaction between indole, Meldrum's acid and polyfunctional, chiral sugar-derived aldehydes occurred with good yield and high diastereoselectivity. We evidenced that the stereochemistry of the newly created stereogenic centre could be controlled by the absolute configuration of the α-carbon in the chiral aldehydes used. However, trimolecular condensation with bicyclic *O*-benzyl-protected aldehyde **3i** afforded the opposite stereochemistry probably via a less congested conformer of the intermediate Knoevenagel product. Further extension of these results may involve the exploration of other chiral aldehydes and the application of three-component condensation products for the synthesis of new polyfunctionalised (tetrahydro)-β-carbolines are of biological interest.

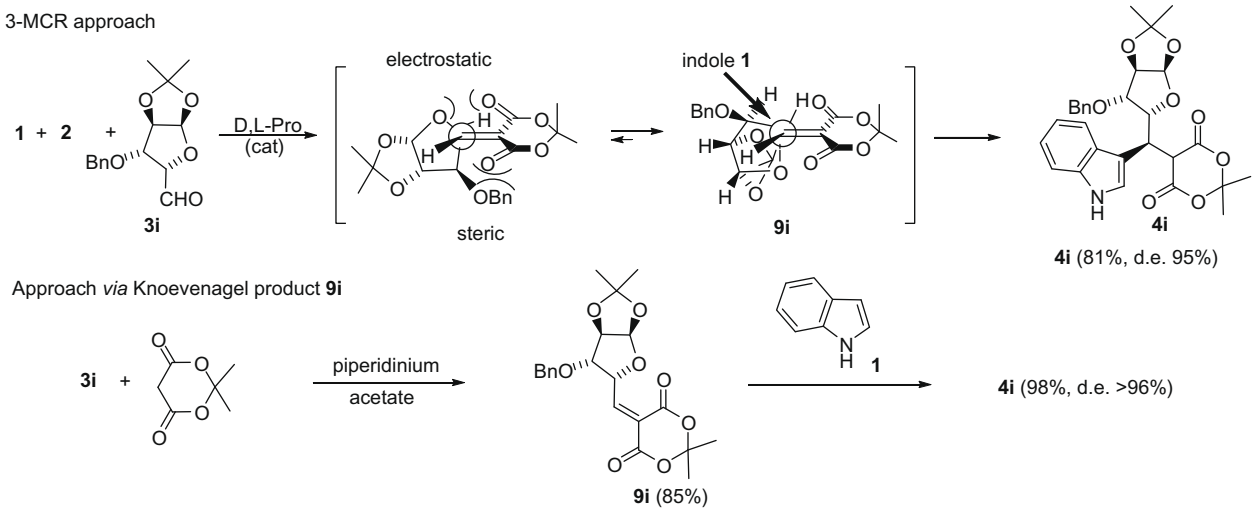
4. Experimental

4.1. General

All solvents were of reagent grade and, when necessary, were purified and dried by standard methods. Reactions and products were routinely monitored by thin-layer chromatography (TLC) on silica gel (Kieselgel 60 F254, Merck). Flash or normal column chromatography purifications were performed on SDS CHROMAGEL® (Silica Gel 60 ACC 35–70 or 70–200 μm). Melting points were determined on a Reichert Thermovar hot-stage apparatus and are uncorrected. UV spectra were recorded in methanol solution on a Unicam 8700 apparatus. IR spectra were measured with a Spectrum BX/RX (Perkin–Elmer) instrument. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on a Bruker AC 300 spectrometer using TMS as internal standard. Couplings expressed as s, sl, d, t and m correspond to singlet, large-singlet, doublet, triplet and multiplet, respectively. Mass spectra were recorded on a MSQ ThermoFinnigan apparatus using electronspray (ESI) or on a GCT Waters apparatus using electronimpact (EI) ionisation method. Optical rotation measurements were carried out on a Perkin–Elmer 241 polarimeter.

4.2. (2*R*,3*S*,4*S*)-2-Benzyloxy-3-*tert*-butyldimethylsilyl-oxy-4,5-dihydroxy-4,5-*O*-isopropylidene-pentanal-1,1-diethyl-dithioacetal 7 and (2*R*,3*S*,4*S*)-3-benzyloxy-2-*tert*-butyldi methylsilyloxy-4,5-dihydroxy-4,5-*O*-*iso*propylidene-pentanal-1,1-diethyl-dithioacetal 8

To a suspension of NaH (60% suspension in oil, 700 mg, 17.5 mmol) in dry THF, were added successively diol **6** (2.00 g, 6.75 mmol) and after 1 h stirring *tert*-butyldimethylsilyl chloride



Scheme 4.

(1.528 g, 10.12 mmol). The reaction mixture was stirred at room temperature for 30 min before adding a catalytic quantity of tetrabutylammonium iodide (35 mg) and then benzyl bromide (2.32 mL, 3.33 g, 19.5 mmol). After one night stirring at room temperature the excess of sodium hydride was quenched at 0 °C by addition of 10% K_2CO_3 solution (20 mL). The aqueous phase was extracted with dichloromethane (3 × 30 mL), the organic phases were dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residue was purified by column chromatography (elution: cyclohexane–CH_2Cl_2 6:4) to give a mixture of **7** and **8** in 77:23 proportion (3.116 g, 92%), as a colourless oil. UV (MeOH) λ_{max} 238, 215 nm; IR (KBr) ν 2951, 2925, 2855, 1454, 1379, 1252, 1207, 1133, 1067, 833, 776, 732, 697 cm^{-1}; NMR data of **7**: ^1H NMR ($CDCl_3$) δ −0.05 (s, 3H), 0.05 (s, 3H), 0.82 (s, 9H), 1.2 (m, 6H), 1.26 (s, 3H), 1.36 (s, 3H), 2.46–2.71 (m, 4H), 3.73 (dd, 1H, J = 3.4, 6.4 Hz), 3.92 (dd, 1H, J = 2.1, 7.8 Hz), 4.04–4.10 (m, 2H), 4.23–4.26 (m, 2H), 4.74 (d, 1H, J = 11.3 Hz), 4.89 (d, 1H, J = 11.3 Hz), 7.25–7.41 (m, 5H) ppm; ^{13}C NMR ($CDCl_3$) δ −4.2, −3.7, 14.3, 14.5, 18.3, 24.4, 24.9, 25.5, 25.8, 26.5, 52.4, 66.4, 73.6, 74.4, 76.2, 82.6, 108.4, 127.3, 127.6, 128.1, 138.5 ppm; MS (CI) *m/z* (%) 500 ($M^{+\cdot}$, 7), 485 (47), 446 (39), 291 (17), 231 (19), 187 (22), 161 (28), 135 (100).

4.3. General procedure for the three-component reaction with sugar-derived aldehydes

Aldehydes were prepared and then directly used for the condensation reaction. To a solution of chiral aldehyde **3** in acetonitrile were added successively indole **1** (1.1 equiv), Meldrum's acid **2** (1.1 equiv) and D,L-proline (0.1 equiv). The reaction mixture was stirred at room temperature under N_2 overnight, the solvent was evaporated and the residue was purified by column chromatography (elution: cyclohexane–ethyl acetate) to afford the title compounds. Chemical yield and diastereomeric excess were determined after chromatography and the major diastereoisomer was then crystallised.

4.4. (1′*S*,2′*S*,3′*R*,4′*S*)-5-[2′,3′,4′,5′-Tetrahydroxy-1′-(1*H*-indol-3-yl)-(2,3:4,5)-di-*O*-isopropylidene-pentan-1′-yl]-2,2-dimethyl-1,3-dioxane-4,6-dione 4d

Isolated by crystallisation from cyclohexane–ethyl acetate (1:1). Mp: 80–82 °C (cyclohexane–ethyl acetate); $[\alpha]_D^{23} = -58$ (c 0.35, $CHCl_3$); UV (MeOH) λ_{max} 290, 281, 274, 222 nm; IR (KBr) ν 3406, 2985, 2937, 2870, 1776, 1743, 1457, 1381, 1324, 1295, 1209, 1152, 1062, 1009, 971, 848, 767, 743 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.29 (s, 3H), 1.30 (s, 3H), 1.36 (s, 3H), 1.38 (s, 3H), 1.39 (s, 3H), 1.68 (s, 3H), 3.84–3.97 (m, 2H), 4.15–4.22 (m, 2H), 4.36 (dd, 1H, J = 9.2, 3.0 Hz), 4.47 (d, 1H, J = 3.0 Hz), 5.08 (dd, 1H, J = 9.2, 7.2 Hz), 7.08–7.27 (m, 4H), 7.66–7.71 (m, 1H), 8.18 (br s, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ 25.6, 26.7, 26.9, 26.95, 27.8, 28.0, 39.8, 49.3, 68.2, 76.9, 82.0, 82.2, 104.9, 108.9, 109.9, 110.8, 112.1, 119.5, 119.6, 121.9, 127.8, 135.2, 165.3, 165.6 ppm; MS (EI) *m/z* (%) 495 ($M^{+\cdot}$+Na, 24), 473 (5), 415 (57), 357 (100). Anal. Calcd for $C_{25}H_{31}NO_8 \cdot 0.5H_2O$: C, 62.23; H, 6.68; N, 2.90. Found: C, 62.17; H, 6.39; N, 3.21.

4.5. (1′*S*,2′*S*,3′*R*)-5-[4′,4′-Bis(ethylsulfanyl)-2′,3′-dihydroxy-1′-(1*H*-indol-3-yl)-2′,3′-di-*O*-isopropylidene-butan-1′-yl]-2,2-dimethyl-1,3-dioxane-4,6-dione 4e

Isolated by crystallisation from ether. Mp: 114–116 °C (ether); $[\alpha]_D^{22} = -50$ (c 1.0, $CHCl_3$); UV (MeOH) λ_{max} 290, 281, 273, 221, 207 nm; IR (KBr) ν 3427, 2978, 2916, 2837, 1780, 1745, 1458, 1384, 1370, 1287, 1216, 1155, 1084, 1049, 1014, 992, 908, 741 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.20 (t, 3H, J = 11.6 Hz), 1.25 (t, 3H, J = 11.6 Hz), 1.42 (s, 3H), 1.43 (s, 6H), 1.69 (s, 3H), 2.54–2.78 (m, 4H), 3.72 (d, 1H, J = 5.0 Hz), 4.03 (d, 1H, J = 3.7 Hz), 4.28 (dd, 1H, J = 6.5, 5.0 Hz), 4.61 (dd, 1H, J = 7.2, 3.7 Hz), 4.99 (dd, 1H, J = 7.2, 6.5 Hz), 7.10–7.20 (m, 2H), 7.16–7.28 (m, 1H), 7.39 (d, 1H, J = 2.7 Hz), 7.66–7.75 (m, 1H), 8.32 (br s, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ 14.1, 14.3, 25.3, 25.4, 27.3, 27.5, 28.0, 28.1, 39.3, 49.3, 53.8, 79.8, 83.2, 105.3, 110.3, 110.4, 111.1, 118.6, 119.9, 122.1, 125.1, 127.5, 135.0, 165.2, 165.3 ppm; MS (EI) *m/z* (%) 529 ($M^{+\cdot}$+Na, 19), 507 (7), 449 (76), 391 (100). Anal. Calcd for $C_{25}H_{33}NO_6S_2$: C, 59.15; H, 6.55; N, 2.76. Found: C, 58.87; H, 6.61; N, 2.95.

4.6. (1′*S*,2′*S*,3′*R*,4′*S*)-5-[2′,3′-Bis(benzyloxy)-4′,5′-dihydroxy-1′-(1*H*-indol-3-yl)-4′,5′-di-*O*-isopropylidene-pentan-1′-yl]-2,2-dimethyl-1,3-dioxane-4,6-dione 4f

Mp: 55–57 °C (cyclohexane–ethyl acetate); $[\alpha]_D^{22} = -144$ (c 0.31, $CHCl_3$); UV (MeOH) λ_{max} 291, 282, 276, 219 nm; IR (KBr) ν 3424, 3356, 2988, 2928, 2886, 1775, 1742, 1456, 1381, 1294, 1211, 1072, 735, 699 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.23 (s, 3H), 1.32 (s, 3H), 1.36 (s, 3H), 1.50 (s, 3H), 3.87 (d, 1H, J = 3.5 Hz), 3.92 (d, 1H, J = 10.5 Hz), 3.98–4.09 (m, 1H), 4.11–4.19 (m, 1H), 4.20–4.24 (m, 2H), 4.41–4.48 (m, 2H), 4.69–4.76 (m, 2H), 4.89 (d, 1H, J = 11.7 Hz), 6.66 (d, 2H, J = 7.7 Hz), 7.02–7.15 (m, 6H), 7.22–7.43 (m, 6H), 7.81–7.85 (m, 1H), 8.31 (br s, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ 24.6, 26.5, 27.5, 27.9, 38.1, 48.6, 65.4, 72.3, 75.0, 77.2, 77.7, 81.6, 104.8, 108.0, 110.7, 113.5, 119.9, 120.2, 122.3, 123.5, 127.4, 127.9, 128.0, 128.1, 128.5, 128.6, 135.3, 137.7, 164.7, 166.5 ppm; MS (EI) *m/z* (%) 611 ($M^{+\cdot}$+Na, 33), 589 (3), 531 (88), 473 (100). Anal. Calcd for $C_{34}H_{39}NO_8$: C, 69.25; H, 6.66; N, 2.37. Found: C, 69.01; H, 6.91; N, 2.55.

4.7. (1′*S*,2′*S*,3′*R*,4′*S*)-5-[2′-Benzyloxy-3′-*tert*-butyldimethylsilyloxy-4′,5′-dihydroxy-1′-(1*H*-indol-3-yl)-4′,5′-di-*O*-isopropylidene-pentan-1′-yl]-2,2-dimethyl-1,3-dioxane-4,6-dione 4g and (1′*R*,2′*S*,3′*R*,4′*S*)-5-[2′-benzyloxy-3′-*tert*-butyldimethylsilyloxy-4′,5′-dihydroxy-1′-(1*H*-indol-3-yl)-4′,5′-di-*O*-isopropylidene-pentan-1′-yl]-2,2-dimethyl-1,3-dioxane-4,6-dione *epi*-4g

A solution of the mixture of thioacetals **7** and **8** (1.882 g, 3.76 mmol) in dry ether (20 mL) was treated with periodic acid (H_5IO_6) (944 mg, 4.14 mmol) at 0 °C and the reaction mixture was stirred at room temperature for 20 min. After quenching with 10% Na_2SO_3 (20 mL) at 0 °C the organic layer was separated and the aqueous phase was extracted with ether (2 × 20 mL). The combined organic layers were dried (Na_2SO_4), filtered and carefully evaporated under reduced pressure. The crude aldehyde mixture **3g**/**3h** was dissolved in dry acetonitrile (20 mL) and to the solution indole **1** (484 mg, 3.76 mmol), Meldrum's acid **2** (596 mg, 3.76 mmol) and D,L-proline (35 mg, 0.3 mmol) were added. After stirring at room temperature for 16 h the solvent was evaporated and the residue was purified by flash chromatography (elution: cyclohexane–ethyl acetate 7:3) affording a mixture (1.602 g, 67%) of four distereomers **4g**, *epi*-**4g**, **4h** and *epi*-**4h**. Major diastereomer **4g** (1.150 g, 48%) was isolated by crystallisation in a mixture of cyclohexane–ethyl acetate (4:1). From the mother liquor minor diastereomer *epi*-**4g** (83 mg, 3%) and the unseparable diastereomeric mixture **4h**/*epi*-**4h** (369 mg, 15%) were isolated by preparative thin-layer chromatography (elution: cyclohexane–ethyl acetate 6:4). Compound **4g**: Mp: 138–139 °C (cyclohexane–ethyl acetate); $[\alpha]_D^{22} = -57.1$ (c 0.3, $CHCl_3$); UV (MeOH) λ 290, 281, 273, 219, 198 nm; IR (KBr) ν 3836, 3396, 2947, 2889, 1776, 1743, 1290, 1248, 1205, 1162, 1086, 1062, 1005, 833, 771, 743 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.01 (s, 3H), 0.25 (s, 3H), 0.88 (s, 9H), 1.32 (s, 3H), 1.36 (s, 3H), 1.51 (s, 3H), 1.65 (s, 3H), 4.02–4.12 (m, 3H), 4.20–4.23 (m, 1H), 4.34–4.44 (m, 4H), 4.68 (m, 1H), 6.74 (d, 2H, J = 6.8 Hz), 7.03–7.30 (m, 7H), 7.79–7.83 (m, 1H), 8.08 (br s, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ −3.4, −3.3, 18.4, 25.3, 26.0,

26.8, 27.8, 28.1, 38.0, 49.1, 66.0, 74.6, 75.1, 75.5, 81.6, 104.9, 108.7, 110.6, 114.0, 119.8, 120.0, 122.1, 123.5, 127.1, 127.7, 127.8, 128.3, 135.2, 138.2, 165.1, 166.0 ppm; MS (EI) *m/z* (%) 660 ($M^{+\cdot}$+Na, 43), 638 (4), 580 (100), 558 (23), 522 (15), 451 (8). HRMS calcd for $C_{35}H_{47}NO_8SiNa$ 660.2969, found 660.2958. Anal. Calcd for $C_{35}H_{47}NO_8Si$: C, 65.91; H, 7.43; N, 2.20. Found: C, 65.70; H, 7.39; N, 2.22. *epi*-**4g**: Mp: 141–142 °C (cyclohexane–ethyl acetate); $[\alpha]_D^{22} = -138.4$ (*c* 0.42, $CHCl_3$); UV (MeOH) λ 291, 281, 274, 223, 213 nm; IR (KBr) *ν* 3427, 2978, 2943, 2881, 1775, 1740, 1458, 1379, 1326, 1296, 1256, 1097, 1067, 1005, 891, 868, 833 cm^{-1}; ^1H NMR ($CDCl_3$) *δ* −0.86 (s, 3H), −0.17 (s, 3H), 0.40 (s, 9H), 1.19 (s, 3H), 1.27 (s, 3H), 1.34 (s, 3H), 1.45 (s, 3H), 3.93–4.03 (m, 3H), 4.19 (dd, 1H, *J* = 7.1, 6.3 Hz), 4.59–4.71 (m, 3H), 4.78 (d, 1H, *J* = 2.7 Hz), 4.99 (dd, 1H, *J* = 10.6, 4.2 Hz), 6.97–7.32 (m, 9H), 7.68–7.70 (m, 1H), 8.05 (br s, 1H) ppm; ^{13}C NMR ($CDCl_3$) *δ* −6.0, −4.9, 17.5, 25.3, 25.4, 26.2, 26.7, 28.0, 38.1, 49.1, 65.0, 72.0, 74.1, 74.8, 81.7, 104.5, 107.8, 110.4, 114.6, 119.4, 119.8, 121.9, 122.8, 127.9, 128.4, 128.5, 135.0, 137.7, 164.9, 166.2 ppm; MS (EI) *m/z* (%) 660 ($M^{+\cdot}$+Na, 32), 638 (7), 580 (100), 558 (10). Anal. Calcd for $C_{35}H_{47}NO_8Si$: C, 65.91; H, 7.43; N, 2.20. Found: C, 65.48; H, 7.59; N, 2.02.

4.8. 5-{(*S*)-[(3a′*R*,5′*R*,6′*S*,6a′*R*)-6′-Benzyloxy-2′,2′-dimethyldihydro-5*H*-furo[3,2-*d*][1,3]dioxol-5′-yl](1*H*-indol-3-yl)methyl}-2,2-dimethyl-1,3-dioxane-4,6-dione 4i

Isolated by crystallisation from cyclohexane–ethyl acetate (4:1). Mp: 157 °C (cyclohexane–ethyl acetate); $[\alpha]_D^{24} = +22.2$ (*c* 0.4, $CHCl_3$); UV (MeOH) λ_{max} 290, 280, 272, 221, 198 nm; IR (KBr) *ν* 3366, 3056, 2982, 2923, 2864, 1775, 1746, 1455, 1381, 1352, 1289, 1211, 1164, 1123, 1097, 1068, 1046, 950, 887, 858, 773, 740 cm^{-1}; ^1H NMR ($CDCl_3$) *δ* 0.90 (s, 3H), 1.33 (s, 6H), 1.56 (s, 3H), 3.35 (d, 1H, *J* = 3.0 Hz), 4.18 (d, 1H, *J* = 3.0 Hz), 4.47 (d, 1H, *J* = 12.0 Hz), 4.54 (dd, 1H, *J* = 10.6, 3.0 Hz), 4.78 (d, 1H, *J* = 4.0 Hz), 4.88 (d, 1H, *J* = 12.0 Hz), 5.32 (dd, 1H, *J* = 10.6, 3.0 Hz), 5.91 (d, 1H, *J* = 4.0 Hz), 7.04–7.47 (m, 9H), 7.73–7.78 (m, 1H); 8.22 (br s, 1H) ppm; ^{13}C NMR($CDCl_3$) *δ* 26.5, 26.9, 27.9, 28.1, 35.8, 48.3, 71.0, 80.4, 81.2, 81.9, 104.8, 105.2, 110.9, 111.7, 112.1, 119.8, 119.9, 122.1, 123.4, 126.7, 128.5, 128.6, 128.8, 135.6, 136.8, 165.1, 169.9 ppm; MS (EI) *m/z* (%) 521 ($M^{+\cdot}$, 65), 494 (15), 463 (8), 419 (21), 377 (23), 346 (15), 329 (28); HRMS calcd for $C_{29}H_{31}NO_8$ 521.2050, found 521.2056.

4.9. (3*S*,4*S*,5*S*)-4-(1*H*-Indol-3-yl)-2-oxo-5-[(1′*S*,2′*S*)-1′,2′,3′-trihydroxypropan-1′-yl]-tetrahydrofuran-3-carboxylic acid methyl ester 5d

To a solution of **4d** (204 mg, 0.43 mmol) in methanol (2 mL) was added a solution of methanol saturated with HCl (5 mL) at 0 °C. After 30 min stirring at room temperature the solvent was removed and the residue was purified by column chromatography (elution: CH_2Cl_2–methanol 9:1) to give **5d** (142 mg, 95%), as a white solid. Mp: 131–133 °C (MeOH–toluene); $[\alpha]_D^{23} = +134.6$ (*c* 0.23, MeOH); UV (MeOH) λ_{max} 290, 281, 274, 221 nm; IR (KBr) *ν* 3410, 2943, 1749, 1723, 1458, 1432, 1379, 1335, 1296, 1229, 1199, 1150, 1093, 1057, 1040, 1009, 996, 750 cm^{-1}; ^1H NMR (CD_3OD) *δ* 3.28 (d, 1H, *J* = 9.4 Hz), 3.41–3.45 (m, 1H), 3.56–3.66 (m, 5H), 4.56 (d, 1H, *J* = 13.1 Hz), 4.71 (dd, 1H, *J* = 13.1, 8.4 Hz), 5.45 (d, 1H, *J* = 8.4 Hz), 7.01–7.20 (m, 2H), 7.27 (s, 1H), 7.31 (d, 1H, *J* = 8.1 Hz), 7.56 (d, 1H, *J* = 7.8 Hz) ppm; ^{13}C NMR (CD_3OD) *δ* 41.7, 52.5, 53.3, 64.4, 71.3, 72.0, 81.8, 109.9, 112.5, 119.2, 120.4, 123.0, 123.6, 128.1, 129.2, 129.9, 138.1, 170.8, 174.9 ppm; MS (EI) *m/z* (%) 349 ($M^{+\cdot}$, 45), 291 (23), 189 (100). Anal. Calcd for $C_{17}H_{19}NO_7$: C, 58.44; H, 5.48; N, 4.01. Found: C, 58.71; H, 5.56; N, 4.30.

4.10. (3*S*,4*S*,5*S*)-5-[2′,2′-Bis(ethylsulfanyl)-(1′*R*)-1′-hydroxyethyl]-4-(1*H*-indol-3-yl)-2-oxo-tetrahydrofuran-3-carboxylic acid 5e

To a solution of **4e** (1.05 g, 2.17 mmol) in tetrahydrofuran (10 mL) was added an aqueous 4 M solution of HCl (5 mL). After two days stirring at room temperature the solvent was removed, the residue was dissolved in dichloromethane (10 mL) and washed with 10% K_2CO_3 solution (3 × 5 mL). The aqueous phase was acidified with solid citric acid and extracted with dichloromethane (3 × 10 mL). The combined organic phases were dried ($MgSO_4$), filtered and evaporated giving **5e** (666 mg, 75%), as a white solid. Mp: 71–72 °C; $[\alpha]_D^{24} = +189.5$ (*c* 0.4, $CHCl_3$); UV (MeOH) λ_{max} 290, 281, 274, 220 nm; IR (KBr) *ν* 3406, 2966, 2918, 1771, 1729, 1457, 1424, 1376, 1338, 1314, 1262, 1233, 1148, 1100, 1009, 743 cm^{-1}; ^1H NMR ($CDCl_3$) *δ* 1.11 (t, 3H, *J* = 11.2 Hz), 1.21 (t, 3H, *J* = 7.6 Hz), 2.31–2.69 (m, 4H), 3.17 (d, 1H, *J* = 10.6 Hz), 3.91 (d, 1H, *J* = 10.6 Hz), 4.50 (d, 1H, *J* = 12.8 Hz), 4.66 (dd, 1H, *J* = 12.8, 8.3 Hz), 5.59 (d, 1H, *J* = 8.3 Hz), 7.09–7.26 (m, 3H), 7.34 (d, 1H, *J* = 7.9 Hz), 7.54 (d, 1H, *J* = 7.6 Hz), 8.25 (br s, 1H) ppm; ^{13}C NMR ($CDCl_3$) *δ* 14.3, 25.4, 26.9, 40.1, 50.5, 55.5, 70.4, 79.2, 109.1, 111.6, 118.3, 120.1, 122.5, 122.6, 126.5, 136.2, 172.4 ppm; MS (EI) *m/z* (%) 399 ($M^{+\cdot}$+Na, 18), 378 (25), 377 (23), 333 (100), 218 (53). Anal. Calcd for $C_{19}H_{23}NO_5S_2{\cdot}0.5H_2O$: C, 54.53; H, 5.78; N, 3.35. Found: C, 54.87; H, 5.70; N, 3.49.

4.11. (3*S*,4*S*,5*S*)-4-(1*H*-Indol-3-yl)-2-oxo-5-[(1′*S*,2′*S*)-1′,2′,3′-trihydroxypropan-1′-yl]-tetrahydrofuran-3-carboxylic acid 5f

A solution of **4f** (142 mg, 0.23 mmol) in ethyl acetate (10 mL) was hydrogenated over 10% PdC (50 mg) for 24 h. The catalyst was removed by filtration on a Celite® pad, the filtrate was evaporated and the residue was purified by chromatography (elution: ethyl acetate–methanol 8:2 and some drops of acetic acid) to afford **5f** (73 mg, 95%), as a white solid. Mp: 192–193 °C; $[\alpha]_D^{24} = +139.3$ (*c* 0.22, acetone); UV (MeOH) λ_{max} 291, 282, 275, 223, 207 nm; IR (KBr) *ν* 3401, 2925, 1740, 1603, 1384, 1344, 1229, 1181, 1089, 1053, 1005, 745 cm^{-1}; ^1H NMR (acetone-d_6) *δ* 3.41 (d, 1H, *J* = 9.1 Hz), 3.51–3.67 (m, 3H), 4.48 (d, 1H, *J* = 12.9 Hz), 4.72 (dd, 1H, *J* = 12.9, 8.7 Hz), 5.45 (d, 1H, *J* = 8.7 Hz), 7.02–7.18 (m, 2H), 7.39–7.45 (m, 2H), 7.70 (d, 1H, *J* = 7.8 Hz), 10.28 (br s, 1H) ppm; ^{13}C NMR (acetone-d_6) *δ* 41.3, 52.1, 64.6, 70.9, 72.1, 80.6, 110.5, 112.3, 119.4, 120.1, 122.7, 123.6, 128.2, 137.6, 170.3, 173.3 ppm; MS (EI) *m/z* (%) 341 ($M^{+\cdot}$+Na, 12), 320 (11), 319 (9), 275 (100), 160 (43). Anal. Calcd for $C_{16}H_{17}NO_6$: C, 60.18; H, 5.38; N, 4.39. Found: C, 59.89; H, 5.70; N, 4.49.

4.12. (3*S*,4*S*,5*S*)-4-(1*H*-Indol-3-yl)-2-oxo-5-[(1′*R*,2′*S*)-1′-*tert*-butyldimethylsilyloxy-2′,3′-dihydroxy-2′,3′-di-*O*-isopropylidene-propan-1′-yl]-tetrahydrofuran-3-carboxylic acid 5g

A solution of **4g** (184 mg, 0.27 mmol) in ethyl acetate (20 mL) was hydrogenated over 10% PdC (50 mg) for 24 h. The catalyst was removed by filtration on a Celite® pad, the filtrate was evaporated to give **5g** (132 mg, 100%), as a white solid. Mp: 76–80 °C; $[\alpha]_D^{25} = +70$ (*c* 0.13, $CHCl_3$); UV (MeOH) λ_{max} 291, 282, 275, 221 nm; IR (KBr) *ν* 3415, 2956, 2927, 1776, 1733, 1633, 1457, 1381, 1257, 1157, 1067, 833, 781 cm^{-1}; ^1H NMR ($CDCl_3$) *δ* −0.09 (s, 3H), −0.01 (s, 3H), 0.85 (s, 9H), 1.22 (s, 3H), 1.23 (s, 3H), 3.67 (dd, 1H, *J* = 7.5, 6.4 Hz), 3.80 (dd, 1H, *J* = 4.9, 4.1 Hz), 3.93–4.02 (m, 2H), 4.05 (d, 1H, *J* = 8.7 Hz), 4.47 (dd, 1H, *J* = 8.7, 7.2 Hz), 5.17 (dd, 1H, *J* = 7.2, 4.1 Hz), 7.10–7.25 (m, 3H), 7.40 (d, 1H, *J* = 8.1 Hz), 7.50 (d, 1H, *J* = 7.5 Hz), 8.40 (br s, 1H) ppm; ^{13}C NMR ($CDCl_3$) *δ* −3.9, −3.7, 18.4, 24.9, 25.9, 26.0, 40.1, 52.7, 66.2, 71.8, 76.0, 82.2, 109.1, 110.6, 111.7, 118.8, 120.4, 122.1, 123.0, 125.9, 136.3, 171.1, 171.6 ppm; MS (EI) *m/z* (%) 511 ($M^{+\cdot}$+Na, 17), 490 (21),

489 (11), 445 (100), 330 (23). Anal. Calcd for $C_{25}H_{35}NO_7Si$: C, 61.32; H, 7.20; N, 2.89. Found: C, 61.09; H, 7.60; N, 3.09.

4.13. (2*S*,3*R*,3a*R*,6*S*,7*S*,7a*R*)-2,3-Dihydroxy-2,3-di-*O*-isopropylidene-7-(1*H*-indol-3-yl)-5-oxo-hexahydro-2*H*-furo[3,2-*b*]pyran-6-carboxylic acid 5i

A solution of **4i** (150 mg, 0.29 mmol) in ethyl acetate (10 mL) was hydrogenated over 10% PdC (50 mg) for 24 h. The catalyst was removed by filtration on a Celite® pad, the filtrate was evaporated to give a mixture of **5i**/**5j** (94:6) (110 mg, 99%) from which **5i** was isolated by crystallisation. Compound **5i**: $[\alpha]_D^{24} = -12$ (*c* 0.88, acetone); ^{1}H NMR (DMSO-d_6) δ 1.29 (s, 3H), 2.10 (s, 3H), 3.68 (dd, 1H, *J* = 12.3, 3.6 Hz), 4.25 (d, 1H, *J* = 12.3 Hz), 4.51–4.58 (m, 1H), 4.89 (d, 1H, *J* = 3.7 Hz), 5.23 (d, 1H, *J* = 2.5 Hz), 6.04 (d, 1H, *J* = 3.7 Hz), 7.00–7.20 (m, 2H), 7.25 (s, 1H), 7.41 (d, 1H, *J* = 7.9 Hz), 7.63 (d, 1H, *J* = 7.9 Hz), 11.10 (s, 1H) ppm; ^{13}C NMR (DMSO-d_6) δ 26.1, 26.5, 36.4, 50.4, 80.6, 81.3, 82.7, 111.5, 112.1, 113.3, 118.5, 119.1, 121.7, 123.0, 125.7, 136.6, 168.8, 169.2 ppm; MS (EI) *m*/*z* (%) 395 ($M^{+\cdot}$+Na, 23), 373 (7), 329 (100), 214 (34).

4.14. (2*S*,3*R*,3a*R*,7*S*,7a*R*)-2,3-Dihydroxy-2,3-di-*O*-isopropylidene-7-(1*H*-indol-3-yl)-hexahydro-2*H*-furo[3,2-*b*]pyran-5-one 5j

A suspension of **5i** (150 mg, 0.40 mmol) in toluene (10 mL) was refluxed for 1 h. After evaporation of the solvent the residue was crystallised from ether to give **5j** (125 mg, 95%) as a white solid. Mp: 182–183 °C (ether); $[\alpha]_D^{24} = -213$ (*c* 0.29, $CHCl_3$); UV (MeOH) λ_{max} 290, 280, 274, 223 nm; IR (KBr) ν 3415, 3386, 2985, 2960, 2937, 2910, 1748, 1624, 1457, 1424, 1381, 1338, 1248, 1224, 1157, 1081, 1052, 1035, 1014, 890, 862, 728 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.31 (s, 3H), 1.45 (s, 3H), 2.82 (dd, 1H, *J* = 16.9, 3.7 Hz), 3.18 (dd, 1H, *J* = 16.9, 6.1 Hz), 3.89–3.92 (m, 1H); 4.59 (d, 1H, *J* = 3.1 Hz), 4.71 (d, 1H, *J* = 3.8 Hz), 4.76 (dd, 1H, *J* = 3.3, 3.1 Hz), 6.05 (d, 1H, *J* = 3.8 Hz), 7.03 (d, 1H, *J* = 3.8 Hz), 7.16–7.29 (m, 2H), 7.42 (d, 1H, *J* = 8.1 Hz), 7.66 (d, 1H, *J* = 8.0 Hz), 8.29 (br s, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ 26.2, 26.6, 30.8, 31.1, 75.9, 82.5, 83.7, 105.1, 111.6, 112.4, 114.3, 118.5, 120.1, 120.9, 122.8, 126.0, 136.3, 169.8 ppm; MS (EI) *m*/*z* (%) 329 ($M^{+\cdot}$, 17), 272 (19), 214 (100). Anal. Calcd for $C_{18}H_{19}NO_5$: C, 65.64; H, 5.81; N, 4.25. Found: C, 65.45; H, 5.84; N, 4.18.

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