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PAPER

Unprecedented stereoselective synthesis of cyclopenta[*b*]benzofuran derivatives and their characterisation assisted by aligned media NMR and ^{13}C chemical shift *ab initio* predictions†

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A new approach to the synthesis of cyclopenta[*b*]benzofuran derivatives *via* reaction of 1,3-dicarbonyl compounds with $\alpha,\beta,\gamma,\delta$-unsaturated aldehydes is described. The constitution and configuration of the new products have been firmly established by means of residual dipolar couplings (RDCs) and *ab initio* ^{13}C NMR chemical shift predictions.

Introduction

The cyclopenta[*b*]tetrahydrobenzofuran core is the basic skeleton present in natural products such as aplysin (**1**)[1] and several members of the flavaglin family (Fig. 1). Recently, increasing attention has been paid to rocaglamide (**2**)[2] and related compounds due to their remarkable antileukemic, insecticidal and cytostatic biological properties which make them promising candidates for medicinal and agricultural applications. In addition, the same heterocyclic core is the base of the chemically stable and pharmacologically useful prostaglandin analogues benzoprostacyclins, such as **3**.[3]

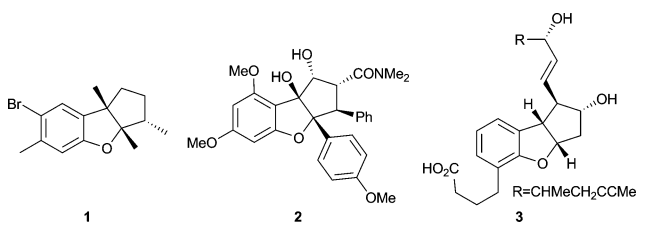

Fig. 1 Natural products with a cyclopenta[*b*]benzofuran skeleton.

Thus, there has been much interest in the development of synthetic methodologies to generate the cyclopenta[*b*]benzofuran system and multiple approaches have been reported,[4] including a recent total synthesis of silvestrol inspired by a biomimetic route.[5] In contrast, the synthesis of partially reduced parent analogues has been little investigated. To the best of our knowledge, reports on their synthesis are based on CAN-mediated oxidative cycloaddition of 1,3-dicarbonyl compounds to different types of olefinic substrates, including vinyl sulfides and cyclic dienes.[6]

Results and discussion

Herein we wish to report a direct and stereoselective entry to the cyclopenta[*b*]benzofuran skeleton *via* a remarkable ring-forming sequence involving the reaction between 1,3-dicarbonyl substrates and $\alpha,\beta,\gamma,\delta$-unsaturated aldehydes.

In order to test the scope of the self-sensitised tandem oxidation process of conjugated enones developed by our group,[7] we attempted the Knoevenagel-type condensation of dimedone (**4a**) and 2-methyl-5-phenyl-penta-2,4-dienal under conventional carbonyl chemistry conditions (piperidine/acetic acid catalysts). Surprisingly, the spectral data of the obtained product were not consistent with the expected trienone **5a** or its 2*H*-pyran valence isomer, but with the tricyclic skeleton **6a**, isolated as a single stereoisomer in 80% yield (Scheme 1). Similar reactivity was observed for 4-hydroxycoumarin (**4b**), stereoselectively yielding the tetracyclic compound **6b** in 46% yield. Apart from slightly reduced yields, the use of other standard Knoevenagel conditions such as EDDA/DCM or even boiling ethanol had no effect on the cyclisation pathway.

Although 2D NMR correlated experiments were consistent with the structures **6a,b**, we were somewhat surprised by the very low field resonance of the carbinol carbon atoms at 104.4 (C3a) and

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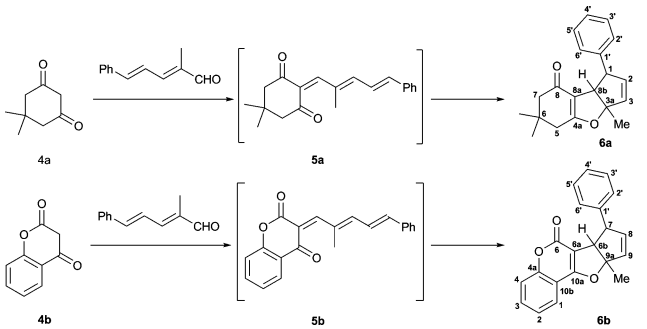
† Electronic supplementary information (ESI) available: copies of ^{1}H and ^{13}C NMR spectra of all products. RDC analysis and measurement tables. Details for ^{13}C chemical shift predictions. DFT computed geometries and energies. See DOI: 10.1039/c1ob05109a



Scheme 1 Stereoselective synthesis of cyclopenta[*b*]benzofuran derivatives **6a** and **6b**.

106.5 ppm (C9a) for **6a** and **6b**, respectively. Besides, the relative stereochemistry of compounds **6** (racemic mixtures) should still be determined as three new stereocenters are created in the cyclisation process, leaving room for four possible diastereomeric relative configurations (Fig. 2).

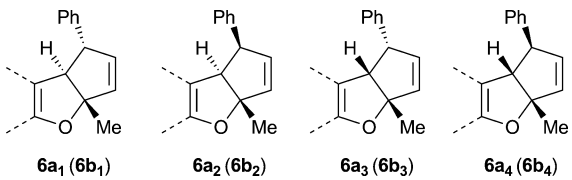
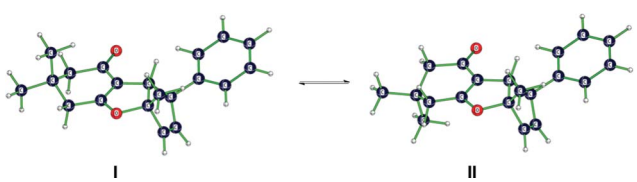


Fig. 2 Possible diastereoisomers for compounds **6a** and **6b**.

To further verify the nature of the new compounds as **6a,b** we have computed ^{13}C chemical shifts by means of DFT GIAO[8] computations. In recent years it has been repeatedly shown that these computations are a complementary tool for the verification of not only chemical constitution but also the relative stereochemistry of organic compounds of natural and synthetic origin.[9] We optimised the structures of all four stereoisomers at the OPBE[10]/6-31G* level of theory. ^{13}C chemical shielding tensors were then computed using this same functional, which, as noted by Xu and coworkers,[11] provides excellent performance at very affordable computational cost. The pcS-1 basis set was employed as it has been specially designed for the DFT computation of chemical shielding tensors.[12]

Due to its high degree of unsaturation the bicyclopentyl moiety of **6a** and **6b** is conformationally rigid but structure **6a** may be present as two different conformers **6a-I** and **6a-II** due to a fast conformational inversion process on the cyclohexenone ring (Scheme 2), and therefore shieldings should be properly averaged. Populations were predicted using the computed OPBE/6-31G* free energies (Table 1). Shifts were obtained from computed shieldings by least-squared fitting to the experimental shifts (see ESI† for details) and the merit of each structure was scored in



Scheme 2 Ring inversion process in **6a**.

Table 1 Root mean square errors (RMSE) in ppm and DP4 probabilities for fitting of predicted OPBE/pcS-1 *vs.* ^{13}C experimental shifts, computed quality factors Q, and OPBE/6-31G* computed relative free energies for all diastereoisomers of **6a-I** and **6b**, and free energies and populations for the (**6a-I**→**6a-II**) conformational equilibrium

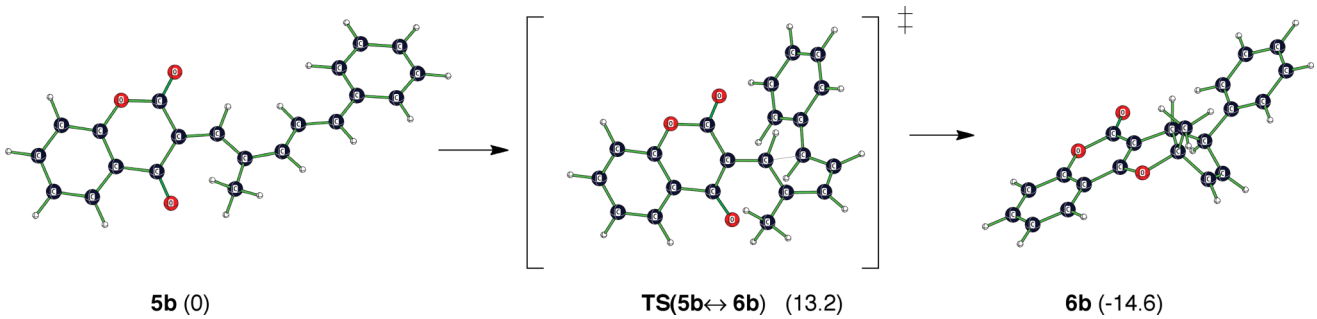
#	Parameter	Configuration			
		1	2	3	4
6a	RMSE	5.0	4.9	3.2	2.4
	DP4	0.0%	0.0%	0.0%	100%
	Q	0.902	0.783	0.542	0.186
	$\Delta\Delta G_{298.15\,K}$	28.1	31.4	3.2	0
	$\Delta\Delta G_{298.15\,K}$ [a]	–0.6 [28]	–0.6 [25]	0.8 [80]	0.1 [44]
6b	RMSE	4.4	4.1	3.1	2.4
	DP4	0%	0%	0%	100%
	Q	0.851	0.473	0.373	0.133
	$\Delta\Delta G_{298.15\,K}$	27.0	30.5	3.3	0

[a] Relative free energies for the **6a-I** → **6a-II** conformational equilibrium and predicted Boltzmann populations (in brackets) for conformer **6a-I** at 298.15 K

terms of the root mean squared error (RMSE) between predicted and observed shifts.

The predicted shifts for the bridgehead α-oxygen carbons C3a and C9a were 106.3 and 107.8 ppm for $\mathbf{6a_4}$ and $\mathbf{6b_4}$, respectively; in very good agreement with the experimental values. Besides, significantly lower RMSEs were obtained for the $\mathbf{6a_4}$ and $\mathbf{6b_4}$ stereoisomers (Table 1). Recently, Goodman has shown that very good discrimination between diastereoisomers from a single experimental spectrum can be obtained with the so-called DP4 probability measurement.[13] DP4 calculates a global probability from individual nucleus error probabilities and therefore is more sensitive to individual errors than global estimators such as the RMSE or the correlation coefficient. Calculation using the published Java applet[14] resulted in a 100% DP4 probability for the $\mathbf{6a_4}$ and $\mathbf{6b_4}$ configurations.

Although the constitution, configuration and conformation of **6a** and **6b** can be determined using conventional NMR experiments (NOE and ^3J analysis), SVD fitting of residual dipolar coupling (RDC) data to a set of judicious structures can unambiguously provide in "one-shot" the correct 3D structure for **6a** and **6b**. The RDC methodology has proven to be a reliable method for the simultaneous characterisation of several stereocenters, especially for rigid or semirigid compounds,[15] and herein we use it as a novel alternative structure verification tool for new synthetic compounds. Although aligned sample preparation is frequently a cumbersome procedure, a new methodology was recently developed[16] for the fast measurement of $^1D_{CH}$ couplings in compressed PMMA gels.[17] Applying the methodology described therein, using a new (bio)degradable PMMA gel derivative with excellent alignment properties (see experimental section), RDCs were obtained at different degrees of alignment and the fitted RDC-slopes for **6a** and **6b** were then analysed by SVD fitting[18] on each of the possible configurations using an in-house version of the MSpin software.[19] The fitness of each stereoisomer was expressed in terms of the quality factor Q.[20] The impact of error measurement was taken into account using a Monte Carlo bootstrapping procedure, with a 512 points Gaussian distribution, assuming a common standard error of 0.5 Hz for all RDCs.[21]



Scheme 3 Thermal cyclisation of **5b**. The relative free energies ($\Delta G_{298.15\,K}$, M06/6-31+G**) of stationary points in kcal mol^{-1} are shown in parentheses.

Although SVD analysis of each structure is straightforward in the case of rigid compound **6b**, the analysis is more complicated in the case of **6a**, due to its conformational mobility, as molecular alignment is not independent from conformation. However, if the conformational change does not largely disturb the overall molecular shape or charge distribution, the so-called single tensor approximation, *i.e.*, decoupling, can be applied with confidence. This introduces the necessity to define a common reference frame for the different conformations.[22] In this particular case we have just, as simple approximation, superimposed the atomic coordinates of the heavy atoms on the two cyclopentyl rings. Boltzmann populations of the two conformations were computed from OPBE $\Delta G_{298.15\,K}$ free energies.

It is noteworthy that RDCs can perfectly differentiate the stereochemistry of these cyclic compounds, giving a very good fit ($Q = 0.186$ and $Q = 0.133$) for $\mathbf{6a_4}$ and $\mathbf{6b_4}$, respectively. In Fig. 3 we have plotted error bars by obtaining the lowest and highest Q factor in the bootstrapping procedure. Fitting of **6b** has associated larger error bars due to the lower number of measured RDCs, but, even in this case, error bars for the lowest-Q solution ($\mathbf{6b_4}$) never overlap with those of the other trial structures. Key NOE cross-correlations from a 900 ms 2D NOESY experiment are shown in Fig. 4. NOE was observed between the methyl and phenyl groups in both **6a** and **6b** compounds in agreement with the RDC and DP4 obtained stereochemistry.

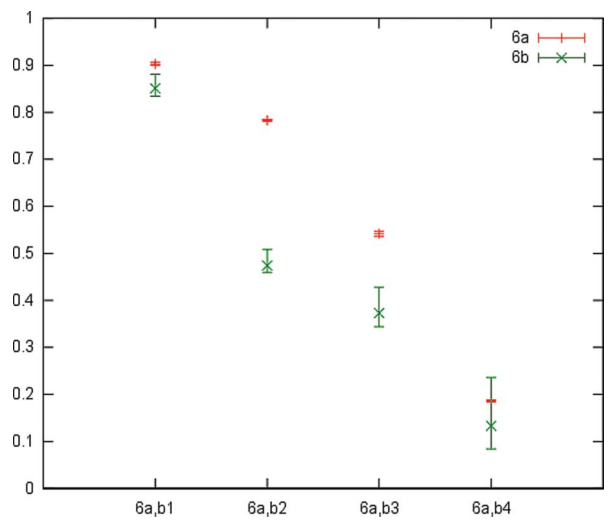


Fig. 3 Quality factors and error bars for RDC fitting of **6a** and **6b** stereoisomeric trial structures.

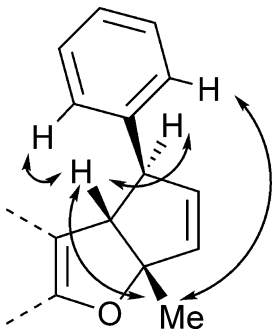


Fig. 4 Relevant observed NOE correlations for compounds **6a** and **6b**.

We envisioned that the stereoselective character of the process depicted in Scheme 1 can be explained in terms of a concerted reaction involving a pentadienyl-cyclopentenyl cation rearrangement. In order to understand the energy profile of the process, we performed a computational study of the cyclisation of trienones **5a** and **5b** at the M06/6-31+G** level of theory. Calculations indicate that the electrocyclic reaction has associated free energy barriers $\Delta G_{298.15\,K}$ of only 14.5 and 13.2 kcal mol^{-1}, respectively.

The transition structure strongly suggests products **6** would arise from trienones **5** *via* a conrotatory 4πe$^-$ electrocyclisation that would also account for the observed stereoselectivity (Scheme 3). Note that the C–O bond is still not formed in the transition structure with an internuclear distance of *ca.* 2.9 Å. However, a second-stage transition structure does not seem to exist and the reaction occurs in a barrierless manner to the final polycyclic product with reaction free energies of –13.3 and –14.6 kcal mol^{-1} for $\mathbf{6a_4}$ and $\mathbf{6b_4}$ formation, respectively. Similar topology for the reaction surface has been described for the mechanism of the Lewis acid catalysed rearrangement of conjugated trienic compounds to bicyclo[3.1.0] structures.[23]

Conclusions

In summary, NMR in aligned media should be considered a viable easy-to-use methodology for the "one-shot" assignment of all stereogenic centers in new synthetic compounds. Further experimental and mechanistic investigations to explore the synthetic potential of the presented ring-forming process are underway.

Experimental section

Chemical reagents were purchased from commercial suppliers and used without further purification, unless otherwise noted. Solvents were analytical grade or were purified by standard procedures prior to use. Yields were calculated for material judged homogeneous by thin layer chromatography and nuclear magnetic resonance (^{1}H NMR). All reactions were monitored by thin layer chromatography (TLC) performed on silica gel 60 F_{254} pre-coated aluminium sheets, visualized by a 254 nm UV lamp, and stained with an ethanolic solution of 4-anisaldehyde. Glassware for reactions was oven-dried at 125 °C and cooled under a dry atmosphere prior to use. Column flash chromatography was performed using silica gel 60 (230–400 mesh). Melting points (m.p.) were taken on an electrothermal melting point apparatus and are uncorrected. Nuclear magnetic resonance spectra were acquired at 300 MHz for ^{1}H and 75 MHz for ^{13}C using $CDCl_3$ as solvent. 2D 900 ms NOESY experiments were collected on a Bruker Avance DMX-500 NMR instrument operating at 500.13 MHz for ^{1}H. Chemical shifts for proton nuclear magnetic resonance (^{1}H NMR) spectra are reported in parts per million relative to the signal of tetramethylsilane at 0 ppm (internal standard) and coupling constants (J) are reported in hertz (Hz). Chemical shifts for carbon nuclear magnetic resonance (^{13}C NMR) spectra are reported in parts per million relative to the center line of the $CDCl_3$ triplet at 76.9 ppm. The following abbreviations are used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, m = multiplet, pent = pentet, hex = hexet, br = broad. IR spectra were obtained using an FT-IR spectrometer and only partial spectral data are listed. High resolution mass spectra (HRMS) were recorded at the University of California Riverside Mass Spectrometry Facility.

2-Methyl-5-phenyl-penta-2,4-dienal

To a stirred solution of cinnamaldehyde (1.0 mL, 7.8 mmol), and propionaldehyde (0.6 mL, 7.8 mmol) in ethanol (7.8 mL) at 0 °C was added NaOH (10% w/v aq., 0.33 mL). The resulting mixture was warmed to room temperature and stirred for 3 days. Then HCl (0.6 N, 0.65 mL) was added. Ethanol was evaporated under reduced pressure and the resulting crude mixture was extracted with ethyl acetate (3 × 5 mL). The combined organic layers were washed with brine (20 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Flash column chromatography (silica gel, hexanes : ethyl acetate, 9.7 : 0.3) afforded aldehyde as a pale yellow solid (729 mg, 54% yield). Mp: 53.5–54.5 °C. IR (KBr): ν_{max}/cm^{-1} 3060, 3036, 3001, 2982, 2921, 2826, 1667, 1616, 1591. ^{1}H NMR ($CDCl_3$, 300 MHz, Me_4Si): δ = 9.44 (s, 1H), 7.49–7.45 (m, 2H), 7.36–7.25 (m, 3H), 7.15 (dd, J = 15.9, 10.6 Hz, 1H), 6.92–6.86 (m, 2H), 1.89 (d, J = 0.9 Hz, 3H) ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 194.3 (d), 148.3 (d), 140.7 (d), 137.2 (s), 135.6 (s), 128.9 (d), 128.4 (2 × d), 127.0 (2 × d), 122.9 (d), 9.1 (q). HRMS: m/z calcd. for $C_{12}H_{12}ONa$ (M + Na$^+$) 195.0780, found 195.0774.

Preparation of 3a,6,6-trimethyl-1-phenyl-1,3a,5,6,7,8b-hexahydro-8*H*-benzo[*b*]cyclopenta[*d*]furan-8-one (6a$_4$)

A mixture of dimedone (250 mg, 1.69 mmol), 2-methyl-5-phenyl-penta-2,4-dienal (290 mg, 1.69 mmol), piperidine (0.022 mL, 0.23 mmol) and acetic acid (0.045 mL, 0.78 mmol) in toluene (15.0 mL) was heated at reflux for 3 h with azeotropic removal of water using a Dean–Stark trap. The mixture was cooled to room temperature and concentrated *in vacuo*. The residue was then purified by flash column chromatography (silica gel, hexanes : EtOAc) to afford the desired compound **6a$_4$** as a colourless oil (397 mg, 80% yield).

IR (film): ν_{max}/cm^{-1} 3059, 3028, 2960, 2928, 1652, 1630, 1028. ^{1}H NMR ($CDCl_3$, 300 MHz, Me_4Si): δ = 7.36–7.28 (m, 4H, Ar–H), 7.23–7.17 (m, 1H, Ar–H), 6.02 (dd, J = 5.7, 2.3 Hz, 1H, 2-H), 5.94 (dd, J = 5.6, 2.0 Hz, 1H, 3-H), 4.04 (q, J = 2.1 Hz, 1H, 1-H), 3.15 (q, J = 1.7 Hz, 1H, 8b-H), 2.26 (d, J = 1.6 Hz, 2H, 5-H), 2.25 (s, 2H, 7-H), 1.57 (s, 3H, 3a-CH_3), 1.101 (s, 3H, 6-CH_3), 1.097 (s, 3H, 6-CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 194.4 (s, C-8), 173.4 (s, C-4a), 143.5 (s, Ar), 137.2 (d, C-2), 133.4 (d, C-3), 128.4 (2 × d, Ar), 127.1 (2 × d, Ar), 126.3 (d, C-4′), 115.4 (s, C-8a), 104.4 (s, C-3a), 56.84 (d, C-1), 56.80 (d, C-8b), 51.0 (t, C-7), 37.8 (t, C-5), 33.8 (s, C-6), 28.5 (q, C6-CH_3), 28.4 (q, C6-CH_3), 25.2 (q, C3a–CH_3). HRMS: m/z calcd. for $C_{20}H_{23}O_2$ (M + H$^+$) 295.1693, found 295.1690.

Preparation of 9a-methyl-7-phenyl-7,9a-dihydro-6*H*,6b*H*-cyclopenta[4,5]furo[3,2-*c*]chromen-6-one (6b$_4$)

A mixture of 4-hydroxy-coumarin (289 mg, 1.75 mmol), 2-methyl-5-phenyl-penta-2,4-dienal (300 mg, 1.75 mmol), piperidine (0.023 mL, 0.24 mmol) and acetic acid (0.047 mL, 0.82 mmol) in toluene (18.0 mL) was heated at reflux for 4 h with azeotropic removal of water using a Dean–Stark trap. The mixture was cooled to room temperature and concentrated *in vacuo*. The residue was then purified by flash column chromatography (silica gel, hexanes : EtOAc) to afford the desired compound **6b$_4$** as a colourless to pale yellow solid (255 mg, 46% yield). Mp: 151.5–152.5 °C (from hexanes : chloroform). IR (KBr): ν_{max}/cm^{-1} 3056, 2980, 2924, 1713, 1645, 1497, 1406, 1067. ^{1}H NMR ($CDCl_3$, 300 MHz, Me_4Si): δ = 7.65 (dd, J = 7.8, 1.6 Hz, 1H, 1-H), 7.54 (td, J = 7.9, 1.4 Hz, 1H, 3-H), 7.39–7.32 (m, 5H, 4-H, 2′-H, 3′-H, 5′-H, 6′-H), 7.29–7.22 (m, 2H, 4′-H, 2-H), 6.12 (dd, J = 5.6, 2.2 Hz, 1H, 8-H), 6.07 (dd, J = 5.6, 1.8 Hz, 1H, 9-H), 4.28 (q, J = 1.9 Hz, 1H, 7-H), 3.48 (d, J = 1.8 Hz, 1H, 6b-H), 1.74 (s, 3H, 9a-CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 163.9 (s, C-10a), 160.4 (s, C-6), 154.8 (s, C-4a), 142.7 (s, C-1′), 137.7 (d, C-8), 133.2 (d, C-9), 132.1 (d, C-3), 128.6 (2 × d, C-3′, C-5′), 127.2 (2 × d, C-2′, C-6′), 126.7 (d, C-4′), 123.6 (d, C-2), 122.9 (d, C-1), 116.8 (d, C-4), 112.9 (s, C-10b), 106.5 (s, C-9a), 105.6 (s, C-6a), 57.4 (d, C-6b), 56.6 (d, C-7), 25.3 (q, C-9a-CH_3). HRMS: m/z calcd. for $C_{21}H_{17}O_3$ (M + H$^+$) 317.1172, found 317.1178.

General experimental procedures for RDC measurements and gel preparation

NMR experiments were collected on a Bruker Avance DMX-500 NMR instrument operating at 500.13 MHz for ^{1}H, 125.77 MHz for ^{13}C and 76.73 MHz for ^{2}H, equipped with a broad band inverse (BBI) probe with only Z gradients and a 2*H*-TX board to perform ^{2}H and ^{1}H 3D gradshimming, and ^{2}H NMR experiments. ^{2}H 1D, ^{1}H 1D, HSQC experiments were collected using standard pulse programs from the Bruker software library. The monomer, methyl methacrylate (MMA, 99%, Aldrich) was purified prior to the experiments by passing the neat liquid through a short column filled with basic alumina in order to

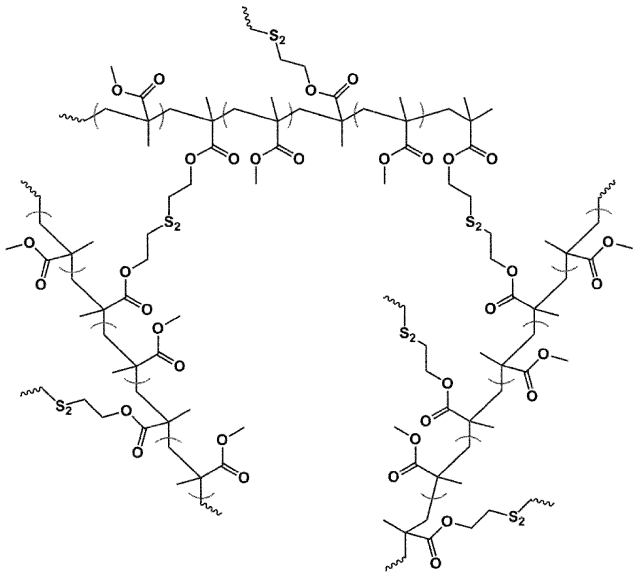


Fig. 5 Structure of the new (bio)degradable PMMA gel derivative with sulfide crosslink used to align compounds **6a** and **6b**.

remove the polymerization inhibitor. The cross-linking agent *bis*(2-methacryloyloxyethyl)disulfide was prepared using a previously published protocol.[24] It was purified prior to use in the same manner as MMA. The radical initiator, V-70 (2,2′-azobis(2,4-dimethyl-4-methoxyvaleronitrile)) was purchased from Wako, and acetone-d_6 and $CDCl_3$ (99.9% degree of deuteration) were purchased from Cambridge Isotope Laboratories.

Preparation of (bio)degradable PMMA-based gels with disulfide crosslinks (Fig. 5). Purified MMA (10 mL) and acetone-d_6 (2 mL) were added to a vial containing V-70 (0.0030 g) and the mixture was stirred until a clear solution was formed. *Bis*(2-methacryloyloxyethyl)disulfide (0.0723 g, 2.5×10^{-4} mol) was added to 10 mL of the above stock solution. The obtained solution was distributed in 3 mm NMR tubes; the tubes were closed with rubber septa and heated in an oil bath thermostated at 50 °C for 5 h. At the end of the polymerization, the tubes were opened and the gels were allowed to dry slowly at ambient conditions. Slow drying is essential for the preparation of uniform rod-shaped gels. When the gels were dry, they shrank and could be easily removed from the tubes. Some tubes had to be broken to take the gels out.

Alignment of compound 6a and 6b using reversible compression/-relaxation of PMMA gels protocol

Two PMMA gel sticks of 2 mm in diameter and 20 mm long with a crosslink density of 0.3 mol % (see above) were inserted into a Wilmad-507-pp-7 5 mm NMR tube. The polymer sticks were swollen and washed according to our previously published protocol.[17] Once the whole set of NMR experiments were collected in isotropic conditions for compounds **6a** and **6b** (2 mg in 500 µl of $CDCl_3$ solution), the volume of each sample was reduced to 100 µl and the samples were transferred into NMR tubes containing the clean and fully relaxed swollen PMMA gel sticks. A Shigemi plunger was inserted into each tube and the gels were compressed and relaxed by pumping them several times with the plunger in order to let the compounds diffuse into the gels. With the gels in the fully relaxed stage, the NMR tubes were inserted into the NMR magnet to verify by ^{1}H NMR that compounds **6a** and **6b** were inside the gel. A series of F2-proton-coupled ^{1}H-^{13}C HSQC experiments were collected at different compression stages. At each compression stage, the position of the plunger was locked by wrapping Teflon tape around the top of the NMR tube. ^{2}H NMR experiments were collected before and after each HSQC experiment to check the quadrupolar splitting (ΔQ_v) of $CDCl_3$ in order to verify that the plunger did not change its position during the experiment. The data extracted from these series of experiments is summarized in ESI Table 1 and 2†. RDCs were plotted against quadrupolar splitting and slopes of the fit to the linear eqn (1) were later used for the alignment tensor analysis with MSpin multiplied by a scale factor of 100.

$$^1T_{CH} = \frac{D}{Q}\Delta Q_v + {}^1J_{CH} \quad (1)$$

Computational details

Stereoisomers **6a,b$_1$** to **6a,b$_4$** were optimized at the OPBE/6-31G* level of theory whereas **5b** thermal cyclization was investigated at the M06/6-31+G** level. Analytical frequencies were computed in all cases to verify the nature of the found stationary points and to compute thermochemical magnitudes. ^{13}C chemical shifts of species **6a,b$_1$** to **6a,b$_4$** were computed at the OPBE/pcS-1 level using GIAO[8] and solvation was taken into account at the PCM[25] level using chloroform parameters. The "fine" pruned (75,302) and "ultrafine" pruned (99 / 590) integration grids were used for OPBE and M06 computations respectively. All computations were performed using the Gaussian09 package.[26]

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