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Synthesis and Raman spectra of 3-deoxy-α-L-rhamnosides as model sugars of the *Ascaris* egg shell

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ABSTRACT

The synthesis of two 3-deoxy-α-L-rhamnosides (i.e., 3,6-dideoxy-L-*arabino*-hexopyranosides) as models of ascaroside natural products is reported. The present approach is based on a Ferrier rearrangement from L-rhamnal, epoxidation of the resulting glycal and reductive opening of the isolated β-epoxide. The 3-deoxy-α-rhamnoside linked to a long aglycone chain was used to ascertain by Raman vibrational spectroscopy the presence of this peculiar sugar in the inner shell of *Ascaris* eggs.

1. Introduction

Ascaris lumbricoïdes, an intestinal roundworm, is one of the most common helminthic human infection worldwide.[1] A number of features account for its high prevalence including ubiquitous distribution, durability of eggs under various environmental conditions, high number of eggs produced per parasite and poor socio-economic conditions that facilitate its spread.[2] Eggs are protected by a shell which might be the more resistant biological structure known to date.[3] Some of us have recently shown that Raman spectroscopy was a valuable technique to give information about the biochemical composition of the shell of *Ascaris* eggs directly in their aqueous environment.[4] Their spectral fingerprints were original with respect to Raman spectra of other micro-organisms (e.g., bacteria and yeasts) already published.[5] Notably, narrow and specific scattering bands could be assigned to ascaroside compounds which consist of 3,6-dideoxy-L-*arabino*-hexose (= ascarylose) linked to a long aglycone chain specific of glycolipids found in the shell of *Ascaris* eggs. Indeed, 3,6-deoxyhexoses play an important role in the structure of major *O*-antigenic determinants isolated from the cell wall lipo-polysaccharides of a number of Gram-negative bacteria.[6] For example, tyvelose (= 3,6-dideoxy-D-mannose) and abequose (= 3,6-dideoxy-D-galactose) were identified from Group B *Salmonella*,[7] colitose (= 3,6-dideoxy-L-galactose) from *Escherichia coli*[8a] or *Vibrio cholerae* O139,[8b] and paratose (= 3,6-dideoxy-D-glucose) from Group A *Salmonella*.[6a] Concerning ascarylose (3,6-dideoxy-L-mannose ≡ the optical antipode of tyvelose), it was first isolated from eggs of *Parascaris equorum* by Fouquey and coll. in 1957.[9] Thirty-nine years later six ascarosides were characterized by Bartley et al.[10] from three fractions, each one composed of two main products, isolated from *Ascaris suum* extracts. The chemical structure of these glycosides is depicted in Figure 1 (fraction A: compounds **1** and **2**; fraction B: compounds **3** and **4**; fraction C: compounds **5** and **6**).

Ascarosides are poorly studied and not commercially available. Moreover, eggs are not cultivable, and the extraction and purification of ascarosides are tedious and give mixtures of compounds. To our knowledge, the published infrared spectra[9a] were not assigned and Raman scattering spectra were not reported in the literature so far. It was then essential to obtain the vibrational spectrum of isolated molecules to assign without ambiguity the spectra of the

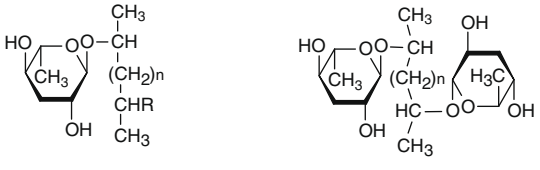

Figure 1. Chemical structures of ascarosides of *Ascaris suum* according to Bartley et al.[10]

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egg shell. Obviously, only the total chemical synthesis of representative ascarosides would allow to obtain vibrational reference spectra for comparison with those of natural ascarosides present in the parasites.[4] Several syntheses of ascarylose,[11] among them some of the corresponding methyl α-glycoside,[11d,e,i,12] have been proposed over five decades but a limited number of syntheses of 3,6-dideoxy-L-*arabino*-hexopyranosides have been reported in the literature.[12b,13] The aim of the present study was to synthesize 3,6-dideoxy-L-*arabino*-hexopyranosides (also called 3-deoxy-α-L-rhamnosides) as models for the in situ identification of ascarosides in the *Ascaris* egg shell.

2. Results and discussion

2.1. Synthesis

Taking advantage of previous works in our laboratory,[14] we decided to explore a new approach based on a Ferrier rearrangement[15] for the glycosylation step (Scheme 1).

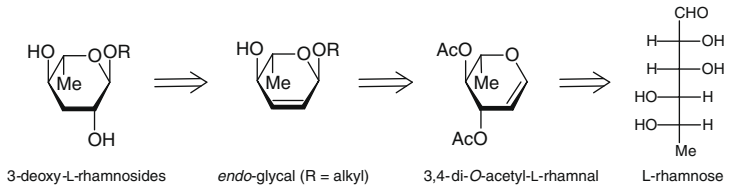
The present approach was first tested with isopropanol [R = CH(Me)$_2$] to avoid problems that might arise from the high hydrophobicity and poor solubility of a fatty alcohol as an acceptor. As previously reported, the reaction of 3,4-di-*O*-acetyl-L-rhamnal **7**[16] with a fourfold excess of isopropanol in the presence of a catalytic amount of BF_3:Et_2O provided mainly the desired 2,3-unsaturated α-*endo*-glycal **8**[17] in good yield (Scheme 2).[18]

A trace of the undesired β-isomer (⩽5%, not depicted here) was formed in these conditions and easily removed by liquid chromatography (LC). Glycoside **8** was deacetylated with K_2CO_3 in MeOH to give alcohol **9** in excellent yield[19] and further alkylated under phase-transfer conditions into benzyl ether **10**. The key-step in the present work was the epoxidation of the double bond to form a 2,3-anhydro-*rhamno* derivative but classical epoxidation conditions (*m*CPBA excess, CH_2Cl_2, $NaHCO_3$)[20] failed to yield a 2,3-anhydro-*rhamno* isomer whatever the nature of the starting 2,3-unsaturated *endo*-glycal **8**–**10** (reaction not described). Only a trace of the undesired *allo*-diastereoisomer **11** could be isolated after 3 days from a sluggish reaction of glycal **9** (R = H) with *m*CPBA at 18 °C (Scheme 3).[21]

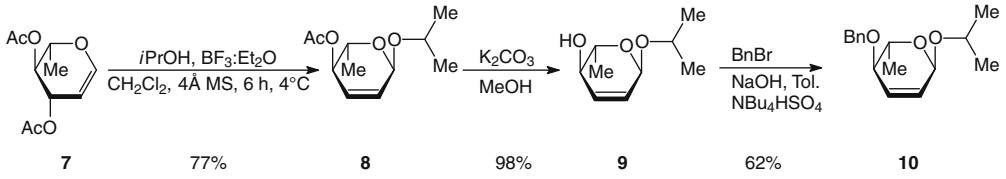
Hydroboration of **9** with BH_3/H_2O_2[22] led only to the recovery of the starting material (vide infra, Scheme 3, left part). According to Payne[23a] and Ferrier,[23b] reaction of the same glycal **9** with a mixture of benzonitrile/H_2O_2 yielded a mixture of diastereoisomeric epoxides which could be easily separated by LC on silica gel. Only the slower moving product **11** crystallized from a saturated chloroform/hexanes solution which allowed structure determination. The X-ray structure of a single crystal of **11** at 110 K[24] confirmed its *syn*-configuration (Fig. 2).

This also confirms that the less polar product **12** has the desired *rhamno* configuration.[25] According to the Furst–Plattner rule,[26] the reductive opening of oxirane **12** with $LiAlH_4$ proceeded regio-selectively[13e,27] to yield first target-compound **13** (Scheme 4).

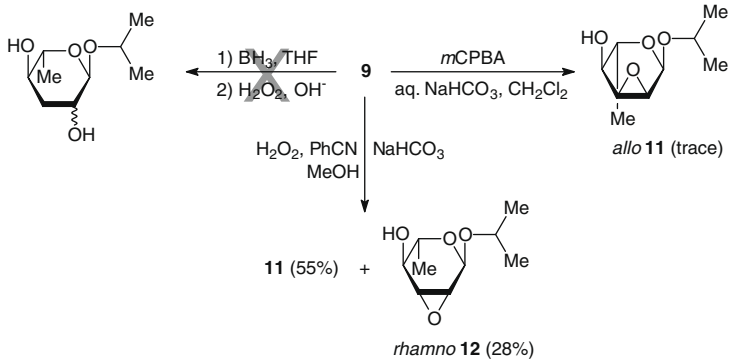
The position of the methylene group in **13** and its acetylated derivative **14** (for further characterization purpose) was established



Scheme 1. Proposed retro-synthesis of 3-deoxy-L-rhamnosides.



Scheme 2. Synthesis of *endo*-glycals from 3,4-di-*O*-acetyl-L-rhamnal.



Scheme 3. Functionalization attempts on *endo*-glycal **9**.

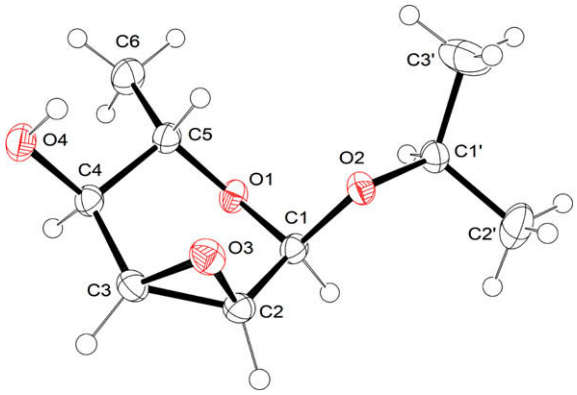
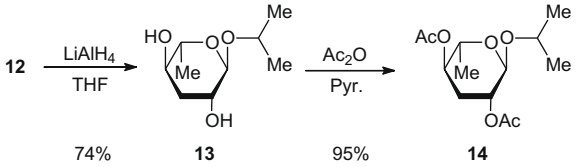
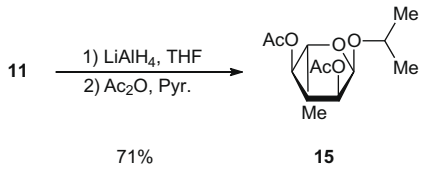


Figure 2. ORTEP view of the X-ray diffraction structure of the *syn*-epoxide **11** with atom-numbering.[24] Thermal ellipsoids are drawn at the 50% probability level. Selected bond lengths and dihedral angles: C1–C2 1.51 Å, C2–C3 1.47 Å, C3–C4 1.51 Å, C4–C5 1.53 Å, C5–O1 1.44 Å, O1–C1 1.43 Å; H1–C1–C2–H2 +13.9°; H2–C2–C3–H3 –0.4°; H3–C3–C4–H4 −46.2°; H4–C4–C5–C6 +170.1°.



Scheme 4. Reductive opening of oxirane **12** and subsequent acetylation.



Scheme 5. Synthesis of 3,6-dideoxy-α-L-*ribo*-hexopyranoside acetate **15** from **11**.

on the basis of ^{1}H NMR spectra by comparison with 3,6-dideoxy-L-*arabino*-hexopyranoside values reported in the literature.[13c,e] In the same manner, the *syn*-epoxide **11** was reduced with $LiAlH_4$ and further acetylated to give the 3,6-dideoxy-L-*ribo*-hexopyranoside diacetate **15** in good yield (71% over two steps, Scheme 5).

A similar synthetic pathway was applied for the synthesis of a lipophilic glycoside but the reaction of L-rhamnal with 2-tricosanol failed under conditions found successful for *i*PrOH (Scheme 6).

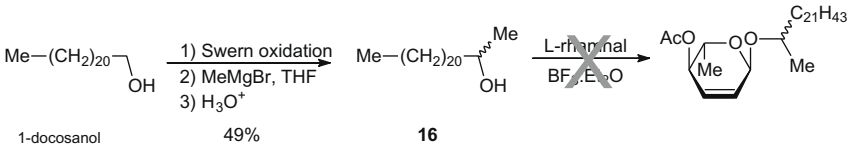
However the reaction of L-rhamnal with commercial 1-docosanol (behenyl alcohol) yielded mainly the α-anomer **17** after 3 h of reaction at 4 °C (Scheme 7).

The major fast-moving α-isomer **17** was easily isolated by LC, quantitatively deacetylated in Zemplén conditions to alcohol **18** which was reacted like *endo*-glycal **9** with H_2O_2/PhCN to give a mixture of epoxides **19** and **20** (Scheme 7). In this case, the *allo*/*rhamno* ratio was ca. 1:1 to be compared with the 2:1 ratio for **11**/**12**, the long aglycone chain likely hindering the attack on the α-side and lowering the overall yield, too. As for the previously depicted epoxide **12**, the regioselective reductive opening of the isolated anhydro-rhamnoside **20** offered the target 3-deoxy-rhamnoside **22** in good yield (80% over three steps, the acetylation step being necessary for purification and characterization purposes, Scheme 8).

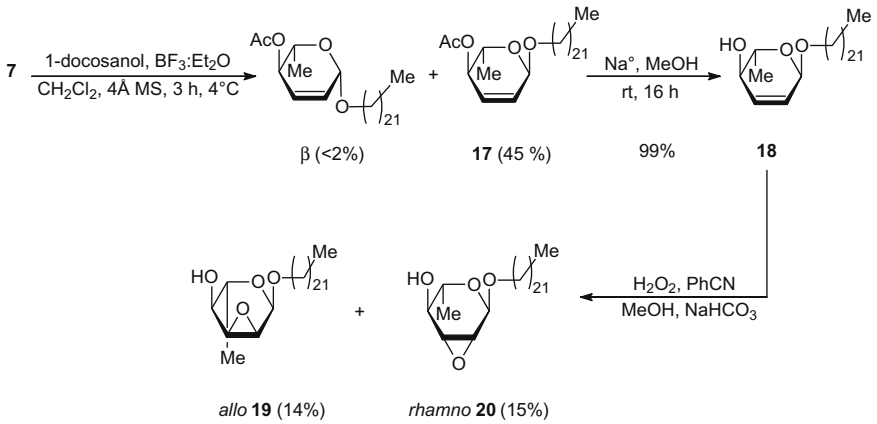
The NMR spectroscopic data of **22** (i.e., δ H-1 & H-2, J_{1-2} & J_{2-3}, $^1J_{C,H}$ value for the C1–H1 bond—see Supplementary data) are in good accordance with those of synthetic ascarosides[13c,e] and of natural ascarosides.[10]

2.2. Raman spectra of 3-deoxy-rhamnosides 13 and 22

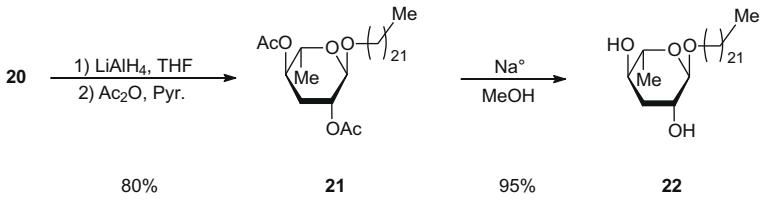
Figure 3 shows the Raman spectra of diols **13** and **22** directly recorded on pure products. Spectra were very cloudy. Tentative assignments of principal bands between 400 and 3600 cm^{-1} were based on assignments previously made for sub-substances available in the literature[28–34] and are gathered in Table 1. The stretching vibration regions of CH and OH groups (3600–2800 cm^{-1}) displayed very different features. Scattering wavenumbers were in accordance with expected bands of the respective aglycone parts. On the one hand, bands from the aglycone-methyl groups



Scheme 6. Synthesis of 1-methyl-docosanol **16** from 1-docosanol.



Scheme 7. Synthesis of epoxides **19** and **20** from **7**.



Scheme 8. Synthesis of 3,6-dideoxy-α-L-*ribo*-hexopyranoside **22** by reductive opening of **20**.

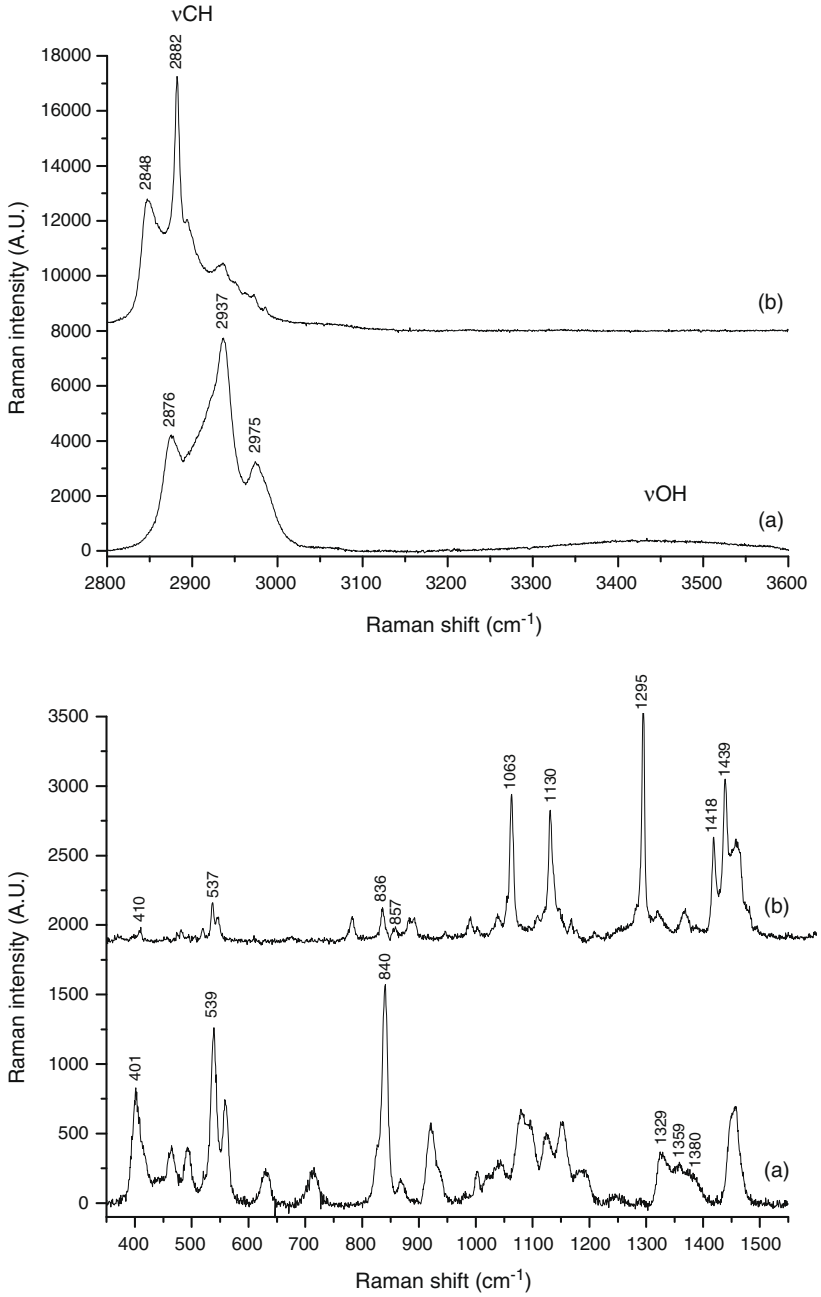


Figure 3. Raman spectra of rhamnosides **13** (a) and **22** (b). Offsets of spectra are used for clarity.

at 2876, 2937 and 2975 cm^{-1} were the major characteristic of the massif between 2800 and 3000 cm^{-1} in the spectrum of **13**.[28] On the other hand, the spectrum of **22** showed major scattering bands at 2848 and 2882 cm^{-1} that are specific for long linear and highly organized CH_2 chains.[29] In the 1200–1500 cm^{-1} region, mainly bending modes of CH_n groups are usually found ($3 \geqslant n \geqslant 1$). Characteristic isopropyl bending modes[28,30] at 1329, 1359 and 1380 cm^{-1} were notably present in the spectrum of **13** (Fig. 3 and Table 1) while three sharp peaks at 1295, 1418 and 1439 cm^{-1} were unambiguously assigned to vibrational modes of

Table 1
Principal scattering Raman bands and tentative assignments in the 400–3800 cm^{-1} region of synthetic compounds **13**, **22** and ascarosides in *Ascaris* eggs (keys: ν: stretching, δ: bending, τ: torsion, ρ: rocking, ω: wagging, a: asymmetric, s: symmetric, *i*Pr: isopropyl, sh: shoulder)

13	**22**	Natural ascarosides[4]	Tentative assignment[28–34]
401	410		δC–C–C (α anomer)
539	537		δC–C–O (α anomer)
631			δC–C–O
713			δC–C–O
	782	785	long CH_2 chain skeleton vibration
840	836	846	νC–C (α anomer)
868	858	857	ρCH_2 pyranose ring
	892		νC–C (CH_3–CH_2) or ρCH_3, long chain
921	883		νC–O–C glycosidic linkage
	990		νC–O, νC–C
1022			δC–O–H
1035	1039		δC–O–H
1042			νC–O
	1063	1063	νC–C, long chain skeleton
1081	1080		δC–O–H
1096	1108		νC–O ring
1124	1121		νC–C, νC–O
	1130	1125	νC–C, long chain skeleton
1133	1146		νC–O pyranose ring
	1168		ρCH_2, long chain
1188	1177		νC–O
	1295	1295	τCH_2, long chain
	1320		δCH
1329			δCH (*i*Pr)
1359			δsCH_3 (*i*Pr)
	1368	1367 (sh)	ωCH_2, long chain
1380			δsCH_3 (*i*Pr)
	1388		δsCH_3
	1418	1416	δCH_2, long chain
	1439	1438	δCH_2, long chain
1450	1451		δsCH_2
1457			δaCH_3 (*i*Pr)
	1460	1458	δCH_2, long chain
	1476		δaCH_2, pyranose ring
	1481		δaCH_3
	2848	2847	νsCH_2, long chain
2876	2860		νsCH_3
	2882	2881	νaCH_2, long chain
	2894		νsCH_2, long chain
	2928		νsCH_2, long chain
2937	2936		2 × δaCH_3
2975	2950; 2963; 2973; 2986	2983	νaCH_3
~3580			νOH

the long linear CH_2 chain[31] in **22** (Table 1). These bands, with those scattering at 1130, 1063 cm^{-1} also assigned to vibrational modes of the CH_2 linear chain, matched well with those observed in the shell of *Ascaris* eggs (Table 1). Between 950 and 1200 cm^{-1}, mainly C-O stretchings often coupled with C–C vibrations from the pyranose ring are scattering. These bands were less intense than those of the aglycone chain because of the higher polarity of the implied bonds in the Raman spectra of **13** and **22** in the anomeric region below 950 cm^{-1}. Interesting bands were present at {401, 539 and 840 cm^{-1}} and {410, 537 and 836 cm^{-1}} in **13** and **22**, respectively. They ascertain the α-glycosidic linkages in both synthesized products.[32] A peak at 846 cm^{-1} is also present in the Raman spectrum of the *Ascaris* eggs periphery[4] supporting the occurrence of α-sugars in the egg shell. In addition, the band at 858 cm^{-1} in the spectrum of **22** is characteristic of the CH_2 rocking mode of the ring-methylene group of a deoxy-sugar.[33] A similar band at 857 cm^{-1} is also observable in the spectrum of *Ascaris* eggs (vide supra, Table 1). All together, scattering matching data ascertain the presence of the same 3-deoxy-α-rhamnoside in both synthetic and natural compounds.

3. Conclusion

The synthesis of two model ascarosides was performed in six steps from L-rhamnal. The Ferrier reaction was successfully used to introduce two alkyl chains on 3-deoxy-L-rhamnose. Epoxidation of *endo*-glycals under the conditions of Payne gave a mixture of oxiranes. Reductive opening of selected oxiranes yielded two new 3-deoxy-α-rhamnosides (i.e., **13** and **22**) which were characterized by conventional spectroscopic methods (^1H and ^{13}C NMR, HRMS). In addition, their Raman vibrational spectra were recorded, compared and finally assigned. Albeit 3-deoxy-rhamnoside **22** is not strictly the major ascaroside present in the eggs of *Ascaris*, lots of significant similarities (e.g., the rare dideoxy-sugar, α-anomery and the long alkyl chain fingerprints) were observed when comparing the in situ spectra of eggs periphery with the Raman spectra of pure **13** and **22**. Finally, taking into account the complexity of the *Ascaris* egg shell, the synthesis of **22** was suitable to ascertain the occurrence of the peculiar 3,6-dideoxy-L-*arabino*-hexose with long-chain aglycones in the egg shell by confocal Raman spectroscopy.

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Supplementary data

Supplementary data (experimental section including spectroscopic data on the synthesised compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.04.061.

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24. *Crystal data for* **11**: $C_9H_{16}O_4$, Mr = 188.22, colourless crystal (0.36 0.24 × 0.12 mm), orthorhombic, space group $P2_12_12_1$ with a = 4.9876(2) Å, b = 9.2229(4) Å, c = 21.6227(11) Å, V = 994.76(8) Å^3, Z = 4, D_c = 1.257 g cm^{-3}, F(0 0 0) = 408, μ = 0.098 mm^{-1}. The final refinement of 125 parameters converged to final R and wR indices $R1$ = 0.0372, $wR2$ = 0.0927 and GOF = 1.034 for 1244 reflections with $I > 2\sigma$ (I), and $R1$ = 0.0446 and $wR2$ = 0.0977 for all unique 1397 data. Data collections of **11** were performed at 110(2) K with MoKα radiation (λ = 0.71073 Å) on an Oxford Diffraction Atlas CCD diffractometer. The structure was solved by direct methods using SHELXS-97 program and refined with full-matrix least-squares on F^2 (G. M. Sheldrick, SHELXL-97 and SHELXS-97, Program for X-ray Crystal Structure Solution and Refinement, (1997) University of Göttingen. All non-hydrogen atoms were refined with anisotropic temperature factors. The hydrogen atoms were placed in calculated positions with their isotropic thermal parameters riding on those of their parent atoms. The residual electronic density ranging from −0.275 to 0.296, with highest positive peak near H2′A atom (0.88 Å). CCDC 748656 contains the supplementary crystallographic data for this Letter. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif, or by e-mailing to data_request@ccdc.cam.ac.uk, or by calling The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(0)1222-336033.
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