

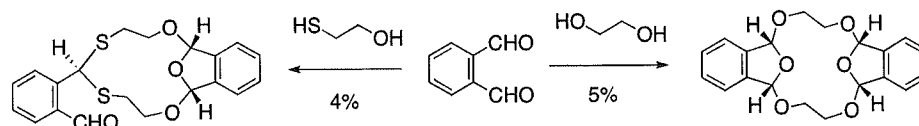
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Novel ether and thioether macrocycles from phthalaldehyde

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Novel ether and thioether macrocycles from phthalaldehyde

R. Alan Aitken^{a*}, Clémence Hauduc^a, Ross S. McLennan^a, Alexandra M. Z. Slawin^a, Heather S. Wilson^a

^aEaStCHEM School of Chemistry, University of St Andrews, North Haugh, St Andrews, Fife, KY16 9ST, U. K.

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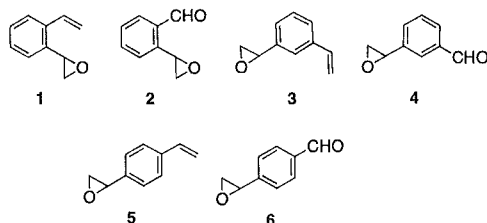
ABSTRACT

By reaction of phthalaldehyde (benzene-1,2-dicarbaldehyde) with ethane-1,2-diol or 2-mercaptoethanol, macrocycles containing respectively 14- and 12-membered polyether/thioether rings were obtained in low but reproducible yield, and their structures confirmed by X-ray diffraction. The simple compounds (2-vinylphenyl)oxirane and 2-oxiranylbenzaldehyde have also been prepared and characterised for the first time.

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In the course of a recent mechanistic study we required access to both (2-vinylphenyl)oxirane (**1**), the monoepoxide of 1,2-divinylbenzene, and its ozonolysis product 2-oxiranylbenzaldehyde (**2**), and were surprised to discover that neither of these simple aromatic compounds has apparently been reported before. In this paper we describe synthetic approaches to these products based on selective reaction of one carbonyl group in phthalaldehyde (benzene-1,2-dicarbaldehyde), which unexpectedly led to new macrocyclic products, as well as the different route to **1** and **2** which was ultimately successful.

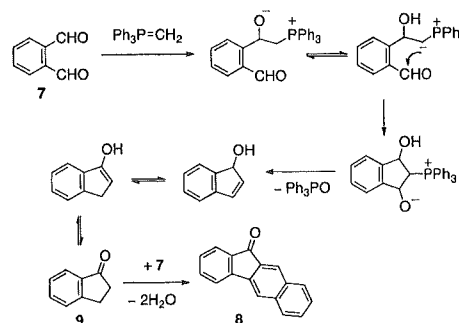
Although neither **1** or **2** have been reported before, there has been work on the regioisomeric compounds. Thus, for example, selective monoepoxidation of 1,3-divinylbenzene to give **3** was achieved using H₂O₂ in the presence of Mo and Sn catalysts,¹ while more recently the same product was formed enantioselectively by asymmetric sulfonium ylide treatment of 3-vinylbenzaldehyde.² Epoxidation of the double bond in 3-



* Corresponding author. Tel. +44 (0)1334 463865; fax +44 (0)1334 463808. E-mail address: raa@st-and.ac.uk (R. A. Aitken)

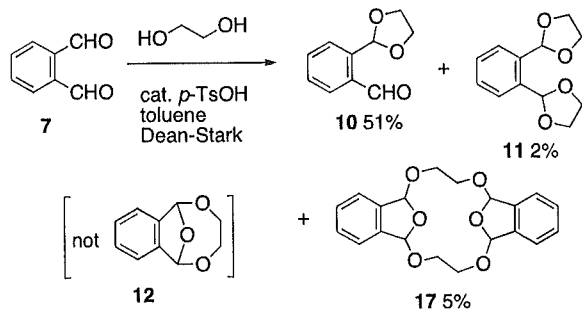
vinylbenzaldehyde using H₂O₂ and a molybdenum catalyst gave compound **4**.³ In the 1,4-series, epoxide **5** has been prepared,⁴ while the aldehyde **6** is also apparently unknown.

Our work began with an attempt to form **2** directly by reaction of the readily available phthalaldehyde (**7**) with one equivalent of dimethylsulfoxonium methylide in DMSO,⁵ but not surprisingly this resulted in cooperative reaction of the adjacent aldehyde functions to give a polymeric product. Interaction of the adjacent aldehyde groups was also observed upon attempted Wittig reaction of **7** using Ph₃P=CH₂ in THF, but in this case a sequence of intra- and inter-molecular reactions resulted in the unexpected formation of benzo[*b*]fluorenone (**8**), obtained in 48% yield after chromatographic purification. The formation of this product, which was readily identified by comparison of its ¹H and ¹³C NMR spectra with literature values,⁶ is rationalised as shown in Scheme 1. Equilibrium transfer of the reactive site from O to C in the initial adduct allows attack at the second aldehyde function and ring closure to give ultimately indan-1-one (**9**), a product which is well known^{7,8} to undergo condensation with **7** under basic conditions to afford **8**. It should be noted that the carbodiphosphorane Ph₃P=C=PPh₃ also reacts directly with **7** to give **8**,⁹ presumably by a similar process.



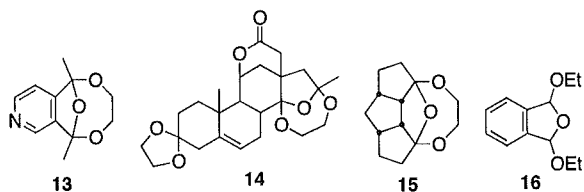
Scheme 1: Proposed mechanism for the formation of **8**

From these studies it became clear that the use of protective groups was more likely to allow successful access to **1** and **2**, so we prepared the monoacetal **10** by reaction of **7** with one equivalent of ethanediol in the presence of catalytic *p*-TsOH under Dean-Stark conditions (Scheme 2). The desired product was obtained in acceptable yield and showed the expected spectroscopic properties,¹⁰ but it was accompanied by a little of the bis(acetal) **11** identified by comparison with literature data,¹¹ and a further previously unknown product.¹²



Scheme 2: Acetal formation from **7**

The NMR spectra showed this to be highly symmetrical with only four ¹H and five ¹³C environments and chemical shifts indicating the presence of a symmetrically 1,2-disubstituted benzene ring together with O-CH-O and O-CH₂CH₂-O functions. The spectra were consistent with the formula **12** and such trioxabicyclo[4.2.1]nonane ring systems have been prepared before by condensation of appropriately configured dicarbonyl compounds with ethanediol, as exemplified by **13–15**.^{13–15}



Phthalaldehyde is also well known to react with ethanol to give the cyclic acetal **16**.¹⁶ However the mass spectrum of the new product showed it to have twice the molecular mass expected for **12** and so most likely to have structure **17**. As far as we are aware this appears to be the first example of macrocycle formation from phthalaldehyde and a diol, although alkoxide-initiated polymerisation to give the polymeric cyclic acetal has been reported.¹⁷

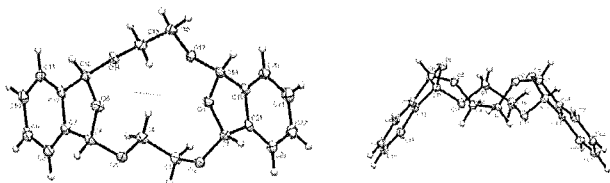
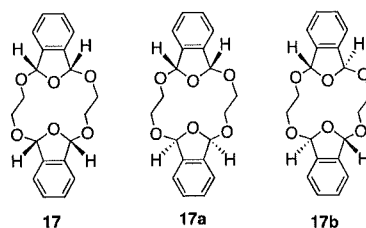


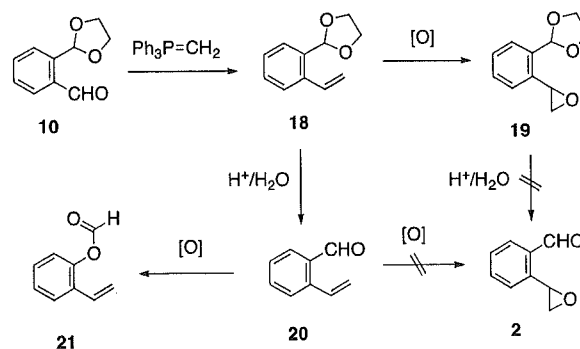
Figure 1: Top and side view of the molecular structure of **17**

The molecular structure of **17** was confirmed by single crystal X-ray diffraction (Figure 1),¹⁸ which also showed the compound to exist exclusively in the *cis-syn-cis* configuration rather than the alternative and apparently less hindered *cis-anti-cis* or *trans-anti-trans* forms **17a** and **17b**. In this configuration the oxygen to oxygen distances across the 14-membered ring macrocycle of **17** are in the range 3.8–4.5 Å, which is lower than the typical values of 4.6–5.0 Å encountered in 15-crown-5 for example,¹⁹ and explains why the compound showed no affinity for metal ions. Attempts to increase the yield of **17** by templating the synthesis

in the presence of various metal salts were uniformly unsuccessful.

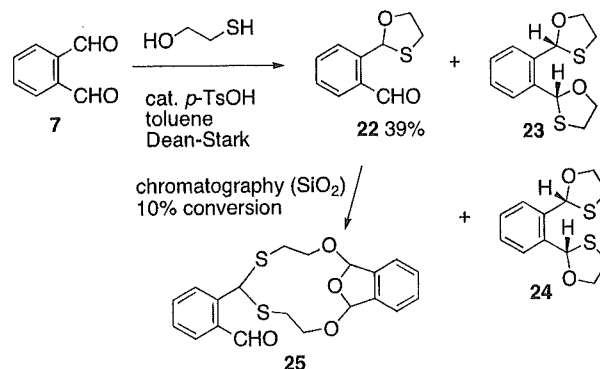


To return to the synthesis of compounds **1** and **2**, Wittig reaction of the aldehyde **10** gave 2-(2-vinylphenyl)-1,3-dioxolane (**18**) whose identity was confirmed by comparison of its ¹H NMR spectrum with the recently reported literature data (Scheme 3).^{12,20} This was successfully epoxidised to compound **19** using *m*-CPBA and **19** was also formed directly when **10** was treated with dimethylsulfoxonium methylide in DMSO. The previously unknown compound **19** gave the expected spectroscopic and HRMS data, including separate ¹³C NMR signals for the slightly non-equivalent dioxolane CH₂ groups,¹² but unfortunately no conditions were found to deprotect the dioxolane function to the aldehyde while leaving the epoxide intact. Removal of the dioxolane from **18** under acidic conditions gave 2-vinylbenzaldehyde **20** but attempted epoxidation of its double bond instead resulted in a Baeyer-Villiger reaction to afford mainly 2-vinylphenyl formate (**21**).²¹



Scheme 3: Attempted formation of **2** starting from **10**

In an attempt to achieve deprotection under milder conditions that would be compatible with the presence of an epoxide we considered using the 1,3-oxathiolane, which can be removed using Raney nickel.²² Treatment of phthalaldehyde with one equivalent of 2-mercaptoethanol in the presence of catalytic *p*-TsOH under Dean-Stark conditions (Scheme 4) resulted in formation of the desired product **22** in reasonable yield.¹²



Scheme 4: Thioacetal formation from **7**

This was accompanied by low yields of two diastereomeric bis(oxathiolanes) **23** and **24**.¹² Chromatographic separation of these products on silica gel also led to formation and isolation of a new crystalline compound that was not present in the crude reaction product. Spectroscopic data were consistent with the macrocyclic aldehyde structure **25** containing a 12-membered ring,¹² and this was confirmed by X-ray diffraction (Figure 2).¹⁸ In this case the larger sulfur atoms led to transannular O–O and O–S distances of only 3.6–4.6 Å making complexation to metal ions unlikely.

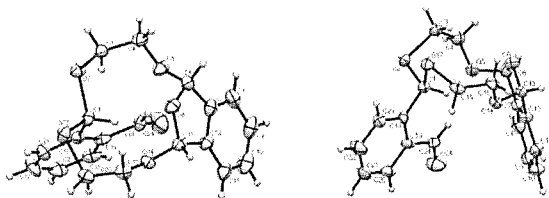
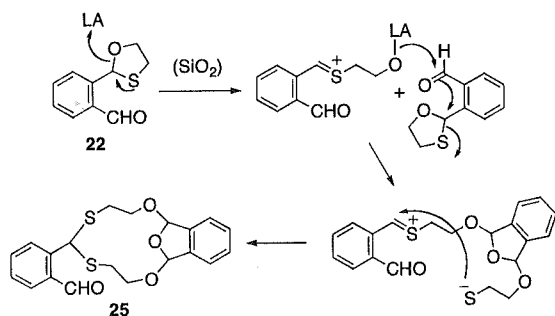


Figure 2: Two views of the molecular structure of **25**

The formation of macrocycle **25** is assumed to result from Lewis acid catalysed dimerisation of the major product **22** on silica (Scheme 5), although attempts to duplicate the process by stirring solutions of either **22** alone, **7** and **23/24**, or **7**, **22** and **23/24** in diethyl ether with silica gel failed with no trace of **25** being formed.



Scheme 5: Proposed mechanism for the formation of **25**

On a single occasion, a crystal selected for X-ray diffraction from a sample of **25** proved to have the new oxathiolane structure **26** (Figure 3),¹⁸ although this compound was present in such a small amount that it could not be detected spectroscopically. The different processes taking place during the chromatographic purification of the products from Scheme 3 are clearly complex and require further study. It should be mentioned that no macrocycle formation was observed on reaction of phthalaldehyde with ethane-1,2-dithiol.

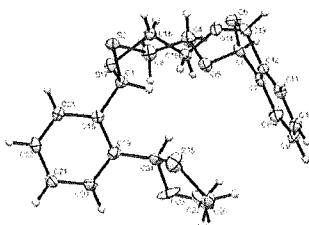
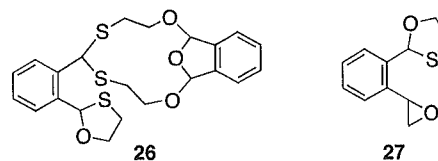
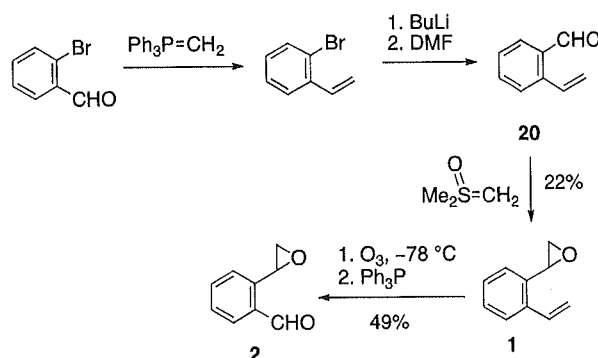


Figure 3: Molecular structure of **26**

Treatment of compound **22** with dimethylsulfoxonium methylide did afford the target epoxide **27**,¹² although in low yield but we were ultimately unable to deprotect this using Raney nickel in acetone to give the epoxy aldehyde **2**.



For the successful synthesis of **1** and **2** we returned to 2-vinylbenzaldehyde (**20**), obtained either by deprotection of **18** as mentioned above, or more efficiently,²³ from 2-bromobenzaldehyde by Wittig reaction with $\text{Ph}_3\text{P}=\text{CH}_2$ followed by lithium/halogen exchange and reaction with DMF (Scheme 6).



Scheme 6: Successful synthesis of **1** and **2**

When the product **20** was reacted with dimethylsulfoxonium methylide, compound **1** was formed in a low but reproducible yield and it was in turn converted into the epoxyaldehyde **2** by ozonolysis in CH_2Cl_2 at -78°C followed by treatment with Ph_3P . Both compounds showed the expected spectroscopic properties,¹² and their use in a study of the mechanism of pyrolysis of benzo[*b*]thiapyran *S,S*-dioxides²⁴ will be reported shortly.

The formation of macrocyclic acetals by condensation of phthalaldehyde with difunctional nucleophiles is a useful new aspect of its reactivity which may also be possible for other compounds containing proximate reactive carbonyl groups.

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- Macrocyclic **17**: colourless crystals, mp 138–139 °C (Found: M^+Na , 379.1147. $\text{C}_{20}\text{H}_{20}\text{O}_6\text{Na}$ (M^+Na) requires, 379.1158); δ_{H} (300 MHz, CDCl_3) 7.38 (8H, s, ArH), 6.19 (4H, s, CH), 4.10–3.90

(8H, m, CH₂); δ_c (75 MHz, CDCl₃) 138.5 (C), 129.5 (CH), 123.1 (CH), 105.8 (CH), 67.5 (CH₂). Vinylidioxolane **18**: colourless liquid; δ_c (75 MHz, CDCl₃) 137.0 (C), 134.2 (C), 133.8 (CH), 129.1 (CH), 127.6 (CH), 126.1 (CH), 125.9 (CH), 116.5 (CH₂), 101.6 (CH), 65.3 (2CH₂). Epoxydioxolane **19**: colourless oil (Found: M+Na, 215.0679). C₁₁H₁₂O₃Na (M+Na) requires, 215.0684; δ_H (300 MHz, CDCl₃) 7.56–7.53 (1H, m, ArH), 7.36–7.30 (3H, m, ArH), 6.06 (1H, s, CH), 4.26 (1H, dd, *J* 4.2, 2.7, CH), 4.14–4.04 (4H, m, 2CH₂), 3.15 (1H, dd, *J* 5.7, 4.2, CH), 2.70 (1H, dd, *J* 5.7, 2.7, CH₂); δ_c (75 MHz, CDCl₃) 136.5 (C), 135.4 (C), 129.4 (CH), 127.6 (CH), 126.2 (CH), 124.4 (CH), 102.1 (CH), 65.3 (CH₂), 65.2 (CH₂), 50.9 (CH), 49.7 (CH₂). Oxathiolane **22**: yellow crystals, mp 39–41 °C (Found: M⁺+Na, 217.0293). C₁₀H₁₀O₂NaS (M⁺+Na) requires, 217.0299; δ_H (300 MHz, CDCl₃) 10.20 (1H, s, CHO), 7.82–7.76 (2H, m, ArH), 7.61–7.56 (1H, m, ArH), 7.49–7.44 (1H, m, ArH), 6.73 (1H, s, CH), 4.65–4.55 (1H, m, OCH₂), 4.05–3.96 (1H, m, OCH₂), 3.18–3.13 (2H, m, SCH₂); δ_c (75 MHz, CDCl₃) 192.3 (CHO), 141.9 (C), 133.8 (CH), 132.9 (CH), 132.4 (C), 128.2 (CH), 126.0 (CH), 83.0 (CH), 72.2 (CH₂), 33.3 (CH₂). Bis(oxathiolanes) **23/24**: (Found: M+Na, 277.0339). C₁₂H₁₄O₂NaS₂ (M+Na) requires, 277.0333; δ_H (300 MHz, CDCl₃) 7.66–7.60 (2H, m, ArH), 7.35–7.32 (2H, m, ArH), 6.34/6.29 (2H, s, CH), 4.65–4.55 (2H, m, CH₂), 3.98–3.89 (2H, m, CH₂), 3.33–3.17 (4H, m, CH₂); δ_c (75 MHz, CDCl₃) 136.44/136.39 (C), 128.71/128.74 (CH), 126.8/126.4 (CH), 83.6/83.8 (CH), 72.0/71.8 (CH₂O), 34.2/34.0 (CH₂S). Macrocycle **25**: colourless crystals, mp 182–184 °C (Found: M+Na, 411.0706). C₂₀H₂₀O₄NaS₂ (M+Na) requires, 411.0701; δ_H (300 MHz, CDCl₃) 10.07 (1H, s), 7.75 (1H, dd, *J* 8, 1.5, ArH), 7.68–7.63 (1H, m, ArH), 7.55–7.45 (5H, m, ArH), 7.33–7.28 (1H, m, ArH), 6.50 (1H, s, CH), 6.18 (2H, s), 4.12 (4H, dd, *J* 6, 5), 3.11 (2H, dt, *J* 15, 5), 2.67 (2H, dt, *J* 15, 6); δ_c (75 MHz, CDCl₃) 191.0 (CHO), 143.4 (C), 138.1 (C), 133.8 (CH), 130.1 (2CH), 129.4 (CH), 128.5 (CH), 127.9 (CH), 123.1 (2CH), 106.1 (2CH), 71.1 (2CH₂), 47.9 (CH), 32.4 (2CH₂) [one quat aromatic C not apparent]. Epoxyoxathiolane **27**: δ_H (300 MHz, CDCl₃) 7.60–7.50 (1H, m, ArH), 7.35–7.25 (3H, m, ArH), 6.35 (1H, s), 4.63–4.57 (1H, m), 4.16 (1H, dd, *J* 4.2, 2.7), 4.02–3.94 (1H, m), 3.30–3.23 (2H, m), 3.17 (1H, dd, *J* 5.7, 4.2), 2.70 (1H, dd, *J* 5.7, 2.7); δ_c (75 MHz, CDCl₃) 137.1 (C), 135.1 (C), 128.7 (CH), 127.9 (CH), 125.6 (CH), 124.4 (CH), 84.2 (CH), 71.9 (CH₂O), 51.0 (CH₂O), 49.7 (CHO), 34.0 (CH₂S). 2-Vinylphenyloxirane (**1**): a very pale yellow liquid, bp 210 °C (oven temp./20 Torr); δ_H (300 MHz, CDCl₃) 7.50–7.45 (1H, m, ArH), 7.30–7.24 (3H, m, ArH), 7.06 (1H, dd, *J* 17, 11, CH), 5.69 (1H, dd, *J* 17, 1, CH₂), 5.38 (1H, dd, *J* 11, 1, CH₂), 4.08 (1H, dd, *J* 4, 3, CH), 3.15 (1H, dd, *J* 6, 4, CH₂), 2.71 (1H, dd, *J* 6, 3, CH₂). δ_c (75 MHz, CDCl₃) 136.8 (C), 134.7 (C), 133.5 (CH=CH₂), 127.9 (CH), 127.8 (CH), 125.7 (CH), 124.5 (CH), 116.9 (CH=CH₂), 50.5 (CH), 50.3 (CH₂). 2-Oxiranylbzaldehyde (**2**): colourless liquid (Found: M⁺+Na, 171.0424). C₉H₈O₂Na (M⁺+Na) requires 171.0422; δ_H

- (400 MHz, CDCl₃) 10.20 (1H, s, CHO), 7.84–7.82 (1H, m, ArH), 7.62–7.58 (1H, m, ArH), 7.54–7.47 (2H, m, ArH), 4.68 (1H, dd, *J* 4, 3, CH), 3.25 (1H, dd, *J* 6, 4, CH₂), 2.61 (1H, dd, *J* 6, 3, CH₂). δ_c (100 MHz, CDCl₃) 192.8 (CHO), 140.1 (C), 134.2 (CH), 134.1 (C), 133.7 (CH), 127.9 (CH), 125.2 (CH), 51.0 (CH₂), 50.4 (CH).
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 18. Compound **17**: C₂₀H₂₀O₆, M = 356.37, monoclinic space group P 2₁; a = 9.253(4), b = 9.129(4), c = 10.515(4) Å, β = 105.373(11)°, V = 856.4(6) Å³, Z = 2, D = 1.382, R = 0.0363 and R_w = 0.0687 for 2436 data with I > 2 σ (I) and 235 parameters. Compound **25**: C₂₀H₂₀O₄S₂, M = 388.50, monoclinic space group P 2₁/c; a = 7.896(5), b = 31.599(16), c = 7.454(4) Å, β = 100.180(15)°, V = 1830.6(17) Å³, Z = 4, D = 1.410, R = 0.143 and R_w = 0.405 for 2963 data with I > 2 σ (I) and 236 parameters. Compound **26**: C₂₂H₂₄O₄S₃, M = 448.61, monoclinic, space group P 2₁/n; a = 9.225(3), b = 7.899(3), c = 28.799(8) Å, β = 92.220(9)°, V = 2097.0(11) Å³, Z = 4, D = 1.421, R = 0.0598 and R_w = 0.1544 for 3141 data with I > 2 σ (I) and 262 parameters. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 1025482 (**17**), 1025483 (**25**) and 1025484 (**26**). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).
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Supplementary Material

Detailed experimental procedures and copies of ¹H and ¹³C NMR spectra for all new compounds.