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Retro-Mannich reactions of 3-alkyl-3,4-dihydro-2*H*-1,3-benz[*e*]oxazines and the synthesis of axially chiral resorcinarenes

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Abstract—Intermediates involved in the conversion of 3-alkyl-3,4-dihydro-2*H*-1,3-benz[*e*]oxazines into 2-*N*,*N*-dialkylaminomethylphenol derivatives, using morpholine and other high boiling secondary amines, have been identified and characterised. Additional experiments have established the involvement of *o*-quinone methide intermediates in the retro-Mannich reactions. Axially chiral resorcinarenes have been prepared by utilising the exchange reactions.

The chemistry of 3-alkyl-3,4-dihydro-2*H*-1,3-benz[*e*]-oxazines, has been studied in some detail.[1–8] Acid-catalysed hydrolyses that result in the formation of secondary amines by loss of formaldehyde,[2,5] undoubtedly result from initial fragmentations to iminium ions. The reductive cleavage of cyclic aminol ethers, including 3-alkyl-3,4-dihydro-2*H*-1,3-benz[*e*]oxazines, for example using formic acid,[7] also involves iminium ion intermediates. Although iminium ion involvement was not discussed, such an intermediate is implicated in the reaction that occurred when 3,8-dimethyl-3,4-dihydro-2*H*-1,3-benz[*e*]oxazine and 2,4-dimethylphenol were mixed and melted at 25°C and which resulted in the formation of a tertiary amine in 87% yield.[4] Fragmentation of the aminol ether moiety to an iminium ion using other electrophiles provides routes to variously functionalised phenols. More recent results have focused on reactions using aprotic conditions. Thus, the interaction of dichlorodimethylsilane with 3-benzyl-6,8-dichloro-3,4-dihydro-2*H*-1,3-benz[*e*]oxazine in the presence of 2-methylfuran gave a tertiary amine in 94% yield.[6] Similarly, a reaction in which 3,4-dihydro-3,6-dimethyl-2*H*-1,3-benz[*e*]oxazine (**1**) was allowed to react with methyltrichlorosilane in the presence of *N*-methylindole, shown in Eq. (1), gave the product **2**[†,‡] in 72% yield and when 3,4-dihydro-3,8-dimethyl-2*H*-1,3-benz-[*e*]oxazine was allowed to interact with methyltrichlorosilane in the presence of *N*-methylindole the expected product, *N*-(2-hydroxy-3-methylbenzyl)-*N*-methyl-(1-methyl-3-indolylmethyl)amine, was obtained in 83% yield.

Keywords: heterocycles; aminol ethers; *o*-quinone methides; axially chiral resorcinarenes.

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† New compounds have been fully characterised by elemental analysis or by accurate mass measurement of the molecular ion by high resolution mass spectrometry and by spectroscopic methods including appropriate ^{1}H and ^{13}C NMR studies on homogeneous material and by infrared measurements.

‡ m/z (M^+) 294.1728, $C_{19}H_{22}N_2O$ requires 294.1732: δ_H 400 MHz ($CDCl_3$) 2.24 (s, 3H, Me), 2.27 (s, 3H, Me), 3.74 (s, 2H), 3.77 (s, 3H, Me), 3.79 (s, 2H), 6.73 (d, 1H, $J=8$ Hz), 6.79 (d, 1H, $J=1.6$ Hz), 6.95 (m, 1H), 7.02 (s, 1H), 7.16 (m, 1H), 7.23 (m, 1H), 7.31 (d×t, 1H, $J=8.0$ and 0.8 Hz), and 7.66 (d×t, 1H, $J=8.0$ and 1.2 Hz) ppm: δ_C 100 MHz ($CDCl_3$) 20.48 (Me), 32.77 (Me), 41.35 (Me), 51.55 (CH_2), 60.46 (CH_2), 109.31 (CH), 109.83 (CH), 115.70 (CH), 118.91 (CH), 119.43 (CH), 121.78 (CH), 121.84 (CH), 127.90 (C), 128.05 (C), 128.86 (CH), 128.93 (CH), 129.00 (CH), 136.94 (C), and 155.60 (C) ppm.

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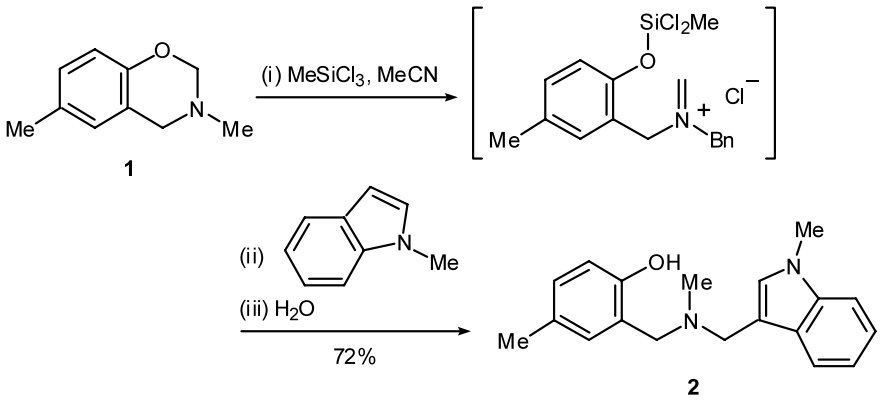
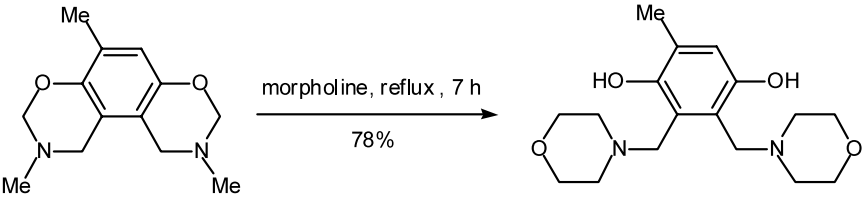


(1)

However, the fragmentation and exchange reactions that involve heating the 3-alkyl-3,4-dihydro-2*H*-1,3-benz[*e*]oxazines with an excess of morpholine that result in the formation of *N*-*o*-hydroxybenzyl morpholine derivatives, exemplified in Eq. (2), are much less well known.[9] The latter reactions are carried out in the absence of electrophilic reagents that are presumably required for the generation of iminium ions. In an earlier study we converted a diastereoisomerically pure resorcin[4]arene derived tetramethoxytetrakis(2-*N*-α-methylbenzyl-3,4-dihydro-2*H*-1,3-benz[*e*]oxazine) into an axially chiral non-racemic derivative, in an overall yield of 33% for the four reactions, by heating the compound in an excess of morpholine for 24 h in order to remove the chiral auxiliary.[10] The high yielding thermally induced exchange reactions, for example of 1-*N*,*N*-dimethylaminomethyl-2-naphthol with morpholine and piperidine,[11] may be related and have been suggested to proceed by Michael addition of the secondary amine to a quinone methide.[12] The involvement of a quinone methide has been implicated further in thermal reactions of 1-*N*,*N*-dimethylaminomethyl-2-naphthol with enamines, such as 1-*N*-pyrrolidinylcyclohexene, and which resulted in the isolation of 1,2-naphthopyran derivatives after treatment with water.[13,14] The capture of other quinone methides by morpholine has also been reported.[15,16] *o*-Quinone methides have also been generated photochemically from Mannich bases derived from phenols including 2-naphthol.[17] *o*-Hydroxybenzyl ethers,[18,19] *o*-[(1-alkylthio)alkyl]phenols,[20] and 2-phenyl-4*H*-1,3,2-benzodioxaborin[21] also have been shown to provide valuable routes to *o*-quinone methides. Recent studies include a computational analysis of *o*-quinone methide towards the prototype nitrogen-, oxygen-, and sulfur-centred nucleophiles, the role of hydrogen bonding and solvent effects,[22] and the preparation of differentially *o*-prenylated phenols.[23] Michael reactions with amines and sulfides, including amino acids and glutathione, have also been studied.[24] We now report the results of a series of experiments designed to delineate the possible reaction pathways involved in the reactions of 3-alkyl-3,4-dihydro-2*H*-1,3-benz[*e*]oxazines with secondary amines together with a series of retro-Mannich reactions including examples that give axially chiral resorcinarenes.

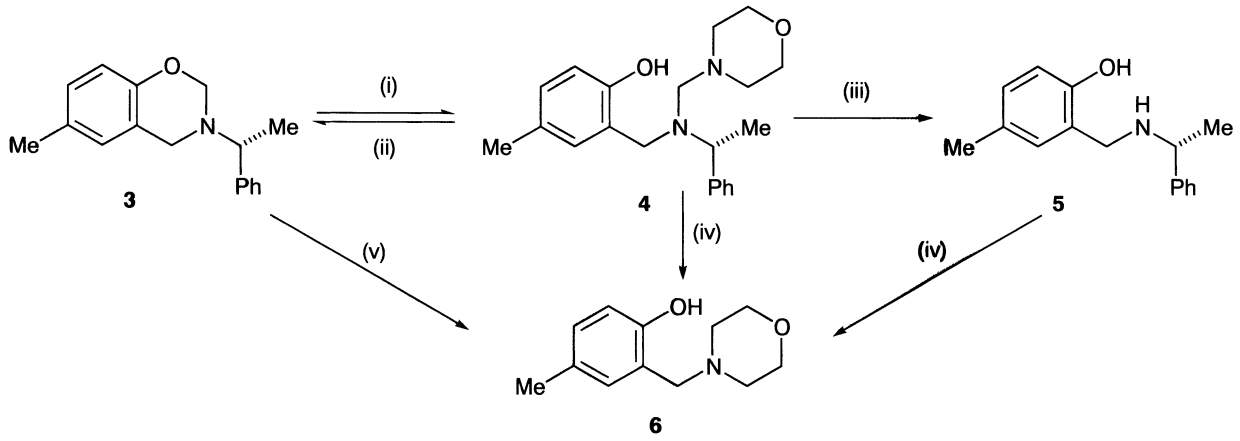
Because of our earlier work, our initial choice of a model compound for the present study was 6-methyl-3-[(1*R*)-1-phenylethyl]-3,4-dihydro-2*H*-1,3-benz[*e*]oxazine **3**, which was prepared in 70% yield by the interaction of *p*-cresol with (*R*)-(+)-α-methylbenzylamine and paraformaldehyde in methanol together with a catalytic amount of potassium hydroxide. When the compound **3** was heated under reflux with an excess of morpholine for 30 min, and then excess morpholine removed under high vacuum, we were able to isolate the unstable aminal **4**[§] in an almost quantitative yield. Although the ^{1}H NMR spectrum was relatively uninformative the ^{13}C NMR spectrum was diagnostic. Chromatography of the aminal **4** on silica gel resulted in its quantitative conversion into the secondary amine **5**[¶], which was also



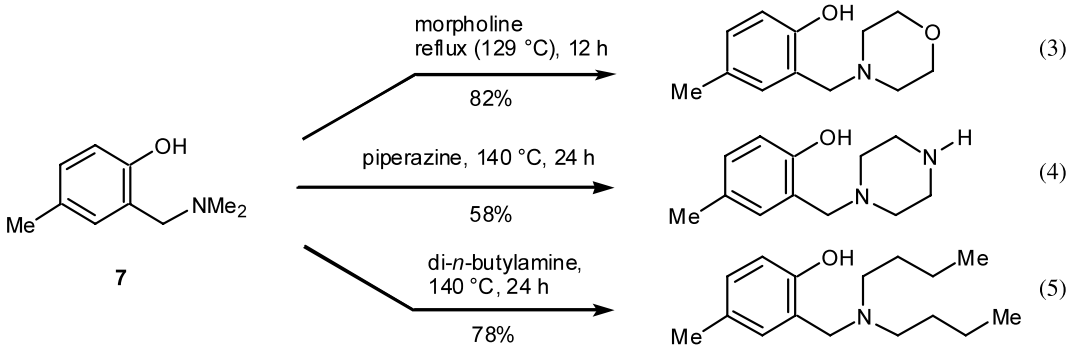
(2)

[§] ν_{max}: 2960, 2852, 1599, 1499, 1452, 1116, and 867 cm^{-1}: δ_C 100 MHz ($CDCl_3$) 20.42 (Me), 23.29 (Me), 50.39 (CH_2), 52.05 (CH_2), 57.28 (CH), 67.06 (CH_2), 81.71 (CH_2), 116.13, 121.43 (C), 126.50 (CH), 127.55 (CH), 128.12 (C), 128.81 (CH), 128.88 (CH), 129.09 (CH), 143.48 (C), and 155.78 (C) ppm.

[¶] *m*/*z* (M^+) 241.14694, $C_{16}H_{19}NO$ requires 241.14666: ν_{max}: 3289, 2967, 1599, 1498, 1252, and 700 cm^{-1}: δ_H 400 MHz ($CDCl_3$) 1.44 (d, 3H, J=7.5 Hz), 2.21 (s, 3H, Me), 3.73 (d, 1H J_{AB}=14.2 Hz), 3.77 (d, 1H, J_{BA}=14.2 Hz), 3.78 (q, 1H, J=7.5 Hz), 6.69 (d, 1H, J=8 Hz), 6.73 (d, 1H, J=1.6 Hz), 6.94 (d×d, 1H, J=8 and 1.6 Hz) and 7.26–7.39 (m, 5H) ppm: δ_C 100 MHz ($CDCl_3$) 14.2 (Me), 23.38 (Me), 50.36 (CH_2), 57.24 (CH), 116.11 (CH), 122.03 (C), 126.94 (CH), 128.41 (CH), 128.48 (C), 128.90(CH), 129.22 (CH), 129.35 (CH), 140.99 (C), and 155.99 (C) ppm.



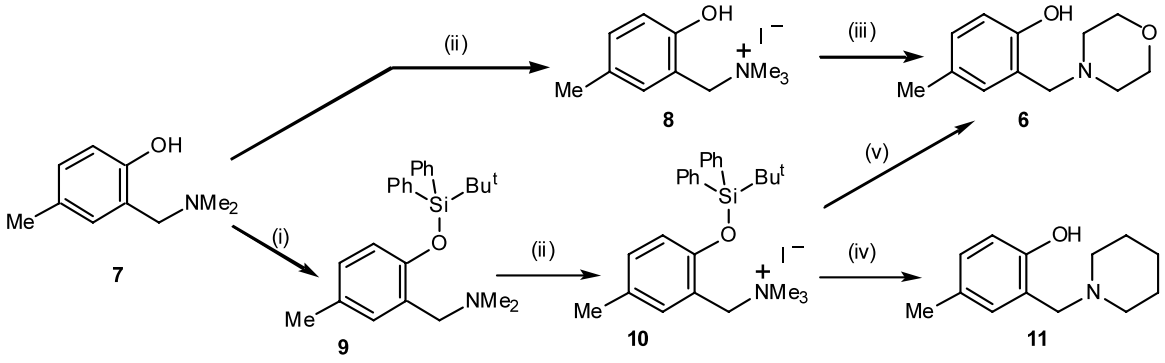
Scheme 1. *Reagents and conditions*: (i) morpholine, reflux, 30 min, 99%; (ii) morpholine, rt, 3 weeks; (iii) silica gel, 100%; (iv) morpholine, reflux, 12 h, 85%; (v) morpholine, reflux 24 h, 51%.



isolated by heating the benzoxazine **3** under reflux in a mixture of ethanol and aqueous hydrochloric acid (5 M). Both the aminal **4** and the secondary amine **5** were converted into 4-methyl-2-*N*-morpholinylmethylphenol **6** in ca. 85% yield when they were heated under reflux in morpholine for 12 h. 6-Methyl-3-[(1*R*)-1-phenylethyl]-3,4-dihydro-2*H*-1,3-benz[*e*]-oxazine **3** gave the tertiary amine **6** in 51% yield using similar reaction conditions. It is interesting to note that after a sample of the aminal **4** was stored at room temperature for 3 weeks it was reconverted into the benzoxazine **3** and morpholine. *N*,*N*-Dimethylbenzylamine does not undergo an exchange reaction when heated under reflux in morpholine for 12 h. These results (Scheme 1) suggest that the intermediates **4** and **5** were converted thermally into 4-methyl-*o*-quinone methide which was captured by morpholine.

We speculated that the reason why morpholine had been chosen most frequently as the secondary amine with which to carry out the exchange reactions is related to the temperature at which *o*-quinone methides are generated from the Mannich bases derived from phenols.[11,15,16] We found, for example, that products from exchange reactions were obtained when 2-*N*,*N*-dimethylaminomethyl-4-methylphenol **7** was heated under reflux in morpholine (82%), or with secondary amines with higher boiling points than morpholine such as piperazine (58% yield), or di-*n*-butylamine (78% yield) (Eqs. (3)–(5)), but not when the Mannich base **7** was heated under reflux in piperidine. The boiling point of piperidine is 106°C whereas that of morpholine is 129°C.

We have also carried out experiments with derivatives of the Mannich base **7**. The amine **7** was converted into its quaternary methiodide **8** in 99% yield. When the quaternary salt **8** was stirred with morpholine at room temperature for 12 h the amine **6** was isolated in 85% yield. Protection of the phenolic hydroxyl group in **7** as the *t*-butyldiphenylsilyl (TBDPS) ether gave the compound **9** in 65% yield and **9** was converted in essentially quantitative yield into the quaternary methiodide **10**. When the compound **9** was heated under reflux in morpholine for 12 h it was recovered in 82% yield. A similar result was obtained when using the quaternary salt **10**. In neither experiment did we detect any product that resulted from direct amine exchange although 4-methyl-2-*N*-morpholinylmethylphenol **6** was formed in 85% yield when the quaternary methiodide **10** was heated under reflux in morpholine for 36 h. We reasoned that the amine **6** resulted from the addition of morpholine to

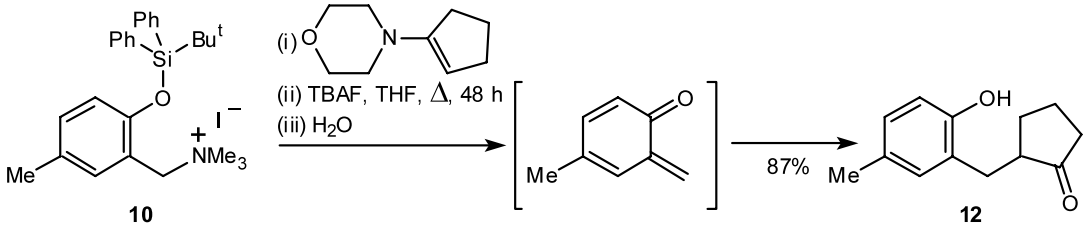


Scheme 2. *Reagents and conditions*: (i) TBDPSCl, Et_3N, DMAP, DCM, 65%; (ii) methyl iodide, Et_2O, 24 h, 99%; (iii) morpholine, rt, 12 h, 85%; (iv) piperidine, TBAF, rt, 12 h, 81%; (v) morpholine, TBAF, rt, 12 h, 100%.

a quinone methide following slow desilylation of the quaternary methiodide **10** induced by iodide ions. The quaternary salt **10** was therefore stirred with an excess of morpholine containing TBAF at room temperature for 12 h after which time the amine **6** was isolated in a quantitative yield. When piperidine was used in place of morpholine in a reaction with the quaternary salt **10**, 4-methyl-2-*N*-piperidinylmethylphenol **11** was isolated in 81% yield. Thus, the involvement of a mechanism involving an *o*-quinone methide is supported by the results of the experiments shown in Scheme 2.

We have also studied reactions of potential quinone methide precursors with enamines. When the quaternary salt **10** was heated for 48 h under reflux in tetrahydrofuran in the presence of TBAF and 1-*N*-morpholinocyclopentene, 2-(2-hydroxy-5-methylbenzyl)-cyclopentanone **12**‖ was isolated in 87% yield after a hydrolytic work-up, as shown in Eq. (6). When we heated 2-hydroxy-5-methyl-*N*-methylbenzylamine and 2-hydroxy-5-methyl-*N*,*N*-dimethylbenzylamine under reflux in xylene with 1-morpholinocyclopentene, followed by a hydrolytic work-up, we obtained 2-(2-hydroxy-5-methylbenzyl)cyclopentanone **12** in 40 and 34% yields, respectively. Although we did not isolate a cyclo adduct in those reactions, spectroscopic data obtained from crude reaction mixtures indicated the presence of a small amount of a cyclic aminol.

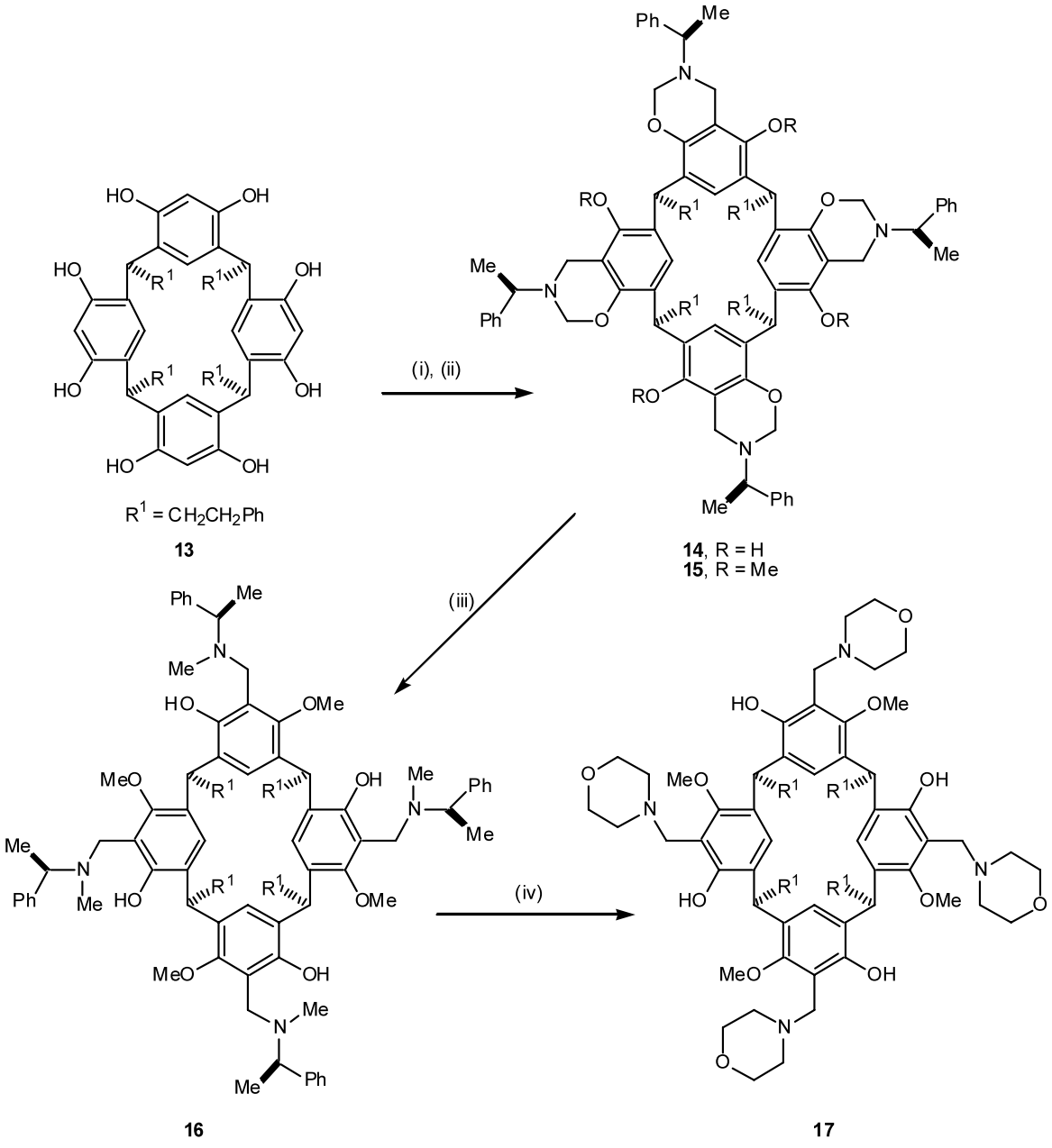
Finally, the C_4 symmetric chiral non-racemic (*R*,*S*)-diastereoisomer **16** was prepared from the achiral C_{4v} symmetric resorcinarene **13** as shown in Scheme 3, using the protocols outlined previously.[10] When the compound **16** was heated under reflux in morpholine it was converted into the chiral non-racemic (*S*)-morpholino-resorcinarene derivative **17**** in 73% yield. Thus, the product **17** was obtained in four steps, each of which involved four identical reactions, in an overall yield of 47% starting from the resorcinarene **13**. In a similar reaction the chiral non-racemic (*S*)-tetra-



(6)

‖ *m*/*z* (M^+) 204.11513, $C_{13}H_{16}O_2$ requires 204.11503: ν_{max}: 3364, 2961, 2873, 1718, 1611, 1510, 1262, 1157, 1125, and 814 cm^{-1}: δ_H 400 MHz ($CDCl_3$) 1.31 (m, 1H), 1.47 (m, 1H), 1.80–1.90 (m, 2H), 2.08–2.22 (m, 2H), 2.27 (s, 3H), 2.40 (m, 1H), 2.48 (m, 1H), 2.77 (d×d, 1H, *J*=12.5 and 5.6 Hz), 2.91 (d×d, 1H, *J*=12.5 and 5.6 Hz), 6.78 (d, 1H, *J*=8.0 Hz), 6.87 (m, 1H), and 6.93 (d×d, 1H, *J*=8.0 and 1.6 Hz) ppm: δ_C 100 MHz ($CDCl_3$) 20.89 (CH_2), 21.27 (Me), 29.34 (CH_2), 29.74 (CH_2), 37.99 (CH_2), 52.12 (CH), 117.29 (CH), 126.22 (C), 128.80 (CH), 129.72 (C), 132.14 (CH), 152.50 (C) and 224.58 ppm.

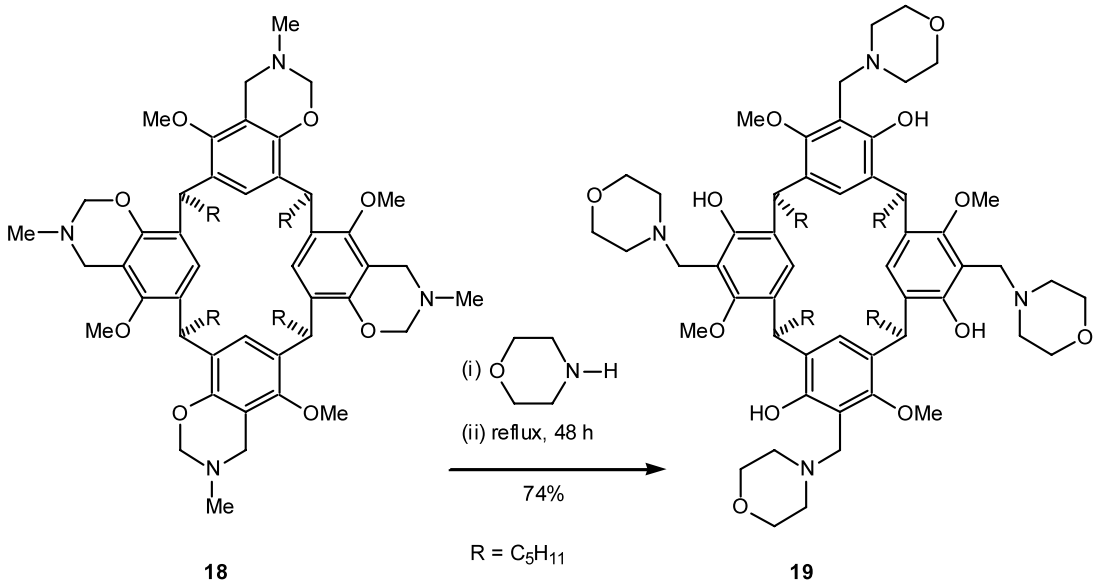
** Mp 146–148°C: $[\alpha]_D^{23}=-30$ (*c* 0.92, $CHCl_3$): Found: C, 80.64; H, 6.95; N, 3.50%; $C_{84}H_{100}N_4O_{12}$ requires C, 80.99; H, 7.07; N, 3.63%: *m*/*z* (FAB) (MH^+) 1357.7466, (M^+) 1356.7407, (MH^+) requires 1357.7416, (M^+) requires 1356.7338: ν_{max}: 3423, 2933, 2852, 2361, 1455, 1117 cm^{-1}: δ_H 400 MHz ($CDCl_3$) 2.04–2.35 (m, 8H), 2.47–2.77 (m, 24H), 3.43 (s, 12H), 3.61–3.77 (m, 24H), 4.61 (t, 4H, *J*=7.4 Hz), 6.86 (s, 4H) and 7.05–7.25 (m, 20H) ppm: δ_C 100 MHz ($CDCl_3$) 34.62 (CH_2), 35.61 (CH), 38.01 (CH_2), 52.83 (CH_2), 55.26 (CH_2), 61.09 (Me), 66.77 (CH_2), 112.66 (C), 125.47 (CH), 125.70 (CH), 127.37 (C), 128.08 (C), 128.19 (CH), 128.42 (CH), 142.78 (C), 154.14 (C) and 154.83 (C) ppm.



Scheme 3. *Reagents and conditions*: (i) *N*,*N*-bis(methoxymethyl)-*N*-(*R*)-(+)-α-methylbenzylamine, EtOH, Δ, 12 h, 83% R = H; (ii) THF, −78°C, *n*-BuLi (5 equiv.), then MeOTf (5 equiv.), then to rt, 94% R = Me; (iii) HCO_2H, Δ, 12 h, 83%; (iv) morpholine, Δ, 48 h, 73%.

kis(benzoxazine) derivative **18** was prepared from the analogue of the compound **16** after removal of the chiral auxiliary by hydrogenolysis using hydrogen in the presence of palladium hydroxide followed by reformation of a tetrakis(benzoxazine) by treatment with formaldehyde. The enantiomer **18** was heated under reflux in morpholine and gave the related chiral non-racemic morpholino-resorcinarene derivative **19** in 74% yield. The final step is shown in Eq. (7) in which the axially chiral (*S*)-enantiomer was converted into the axially chiral (*R*)-product.

In summary we have established the nature of the intermediates involved in the fragmentation-exchange reactions of 3-alkyl-3,4-dihydro-2*H*-1,3-benz[*e*]oxazines and made use of the processes in the synthesis of the resorcinarene derivatives **17** and **19**, both of which possess only axial chirality.



(7)

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