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Rapid Development of an Enantioselective Synthesis of (*R*)-1-Hydroxy-7-methoxy-1,2,3,4-tetrahydronaphthalene-1-carboxylic Acid

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Abstract:

A two-stage, three-step synthesis of (*R*)-1-hydroxy-7-methoxy-1,2,3,4-tetrahydronaphthalene-1-carboxylic acid from 7-methoxy tetralone is described which employed an optimised Wittig olefination of 7-methoxytetralone and Sharpless asymmetric dihydroxylation followed by platinum-catalysed oxidation.

α-Hydroxycarboxylic acid **4**, a key intermediate in a drug candidate synthesis, was required in multigram quantities to facilitate our research and development program. The compound had previously been synthesised from 7-methoxytetralone **1** using the TMS−cyanohydrin **2** as detailed in Scheme 1.[1] Closer inspection of the route highlighted several potential problems for scale-up; for example in step 1, the preparation of **2** utilised TMSCN. Although it is possible to use TMSCN both in our laboratories and pilot plant, this reagent is not particularly amenable for usage at most scale-up facilities and requires that special safety precautions be followed. In addition, a literature review at the time (October 1998) revealed few examples of the asymmetric addition of cyanide to ketones. Enzymatic methods[2] were limited to a small number of aromatic ketone substrates, and often gave meagre chemical yields (>15%). Transition-metal-catalysed methods employed high pressures (0.8 Gpa), and only low-to-moderate enantiomeric excess was achieved.[3] Therefore, rapid development of an asymmetric variant of the route was going to be difficult.[4] The next stage in the synthesis was a multistep low-yielding hydrolysis[5] of TMS−cyanohydrin adduct **2**, from which the resulting alcohol, **3**, was isolated after preparative chromatography. The major side products from the hydrolysis were the starting tetralone (formed by the retro-cyanohydrin reaction), intermediate hydrolysis products, and various unsaturated compounds formed by elimination of water. Finally, after base hydrolysis of **3**, the next stage in the synthesis was the coupling of the racemic acid with an expensive homochiral amine. Separation of the resulting two diastereoisomers by preparative HPLC gave the required diastereomer, **5**.

After consideration of these factors, we decided that not only was the route unsuitable for large-scale manufacture but it was also unlikely to be able to provide sufficient quantities of **4** to meet the demands of our development program.[6] Therefore, development of a new route was undertaken. Rapid evaluation of several alternative routes, both enantioselective and racemic, identified the synthetic sequence outlined in Scheme 2 for further development. Other asymmetric routes to the alcohol **7** were also considered. For example, preparation of a chiral epoxide from **1**, using chiral iminium salts[7] or Jacobsen epoxidation,[8] followed by ring opening of the epoxide gave **7**. However, because of time constraints, these routes were not investigated in the laboratory.

Olefination. Initial quantities of the exomethylene compound, **6**, were prepared using standard Wittig conditions.[9] 7-Methoxytetralone was treated with 2 equiv of preformed $Ph_3P{=}CH_2$ (from Ph_3PMeBr, BuLi, THF, −40 °C), providing access to **6** in 62% isolated yield after chromatography. Unreacted tetralone **1** constituted the balance of material. Attempts to improve the yield of **6** using these reagents proved unsuccessful. The mode of addition (ketone addition to ylide vs addition of ylide to ketone) showed no difference in reaction. Use of different solvents (toluene and MTBE) also had little effect. The best conversion was observed in DME (85% wrt **1**); however, work-up led to some isomerization of **6** to give by-product **8** (Scheme 3), a problem that we anticipated would become more significant upon scale-up.[10] The ratio of ylide to tetralone **1** was also examined. Use of 1, 2, and 3 equiv of ylide in the reaction gave identical HPLC profiles, and increasing reaction times had no effect on the conversion of **1** to **6**. ReactIR experiments confirmed

(1) Bigge, C. F.; Malone, T. C.; Hays, S. J.; Johnson, G.; Novak, P. M.; Lescosky, L. J.; Retz, D. M.; Ortwine, D. F.; Probert, A. W., Jr.; Coughenour, L. L.; Boxer, P. A.; Robichaud, L. J.; Brahce, L. J.; Shillis, J. L. *J. Med. Chem*. **1993**, *36*, 1977. Inghardt, T., Karlsson, O.; Linschoten, M.; Nystrom, J. PCT Int. Appl. WO 0035869, 2000, 102 pp. Karlsson, O.; Linschoten, M.; Nystrom, J. PCT Int. Appl. WO 9857932, 1998, 120 pp.

(2) Effenberger, F.; Horsch, B.; Weingart, F.; Ziegler, T. *Tetrahedron Lett*. **1991**, *32*, 2605. Effenberger, F.; Heid, S. *Tetrahedron Asymmetry* **1995**, *6*, 2945. Foerster, S.; Roos, J.; Effenberger, F.; Wajant, H.; Sprauer, A. *Angew. Chem., Int. Ed. Engl*. **1996**, *35*, 437. Kiljunen, E.; Kanerva, L. T. *Tetrahedron Asymmetry* **1997**, *8*, 1551. Griengl, H.; Klepier, N.; Pochlaur, P.; Schmidt, M.; Shi, N.; Zabelinskaja-Mackova, A. *Tetrahedron* **1998**, *54*, 14477.

(3) Choi, M.C. K.; Chan, S. S.; Matsumoto, K. *Tetrahedron Lett*. **1997**, *38*, 6669 and references therein.

(4) For some recent examples of asymmetric addition of cyanide to aromatic ketones, see: Deng, H. Isler, M.P.; Snapper, Hoveyda, A. H. *Angew. Chem., Int Ed.* **2002**, *41*, 1009 and references therein.

(5) A range of acidic and basic hydrolysis conditions were shown to be inefficient in effecting the direct transformation of **2** to **4**.

(6) The first delivery of material (5 kg) for use in subsequent steps was required in 2 months from the start of the compound entering development.

(7) Aggarwal, V.K.; Wang, M. F. *Chem. Commun*. **1996**, 191.

(8) Zhang, W.;Loebach, J. L.; Wilson, S. R.; Jacobsen, E. N. *J. Am Chem. Soc*. **1990**, *112*, 2801.

(9) Moutiers, G.;El Fahid, B.; Goumont, R.; Chatrousse, A. P.; Terrier, F. *J. Org. Chem*. **1996**, *61*, 1978−1985.

(10) Our main concern was loss of yield in the subsequent dihydroxylation step if **6** contaminated with large amounts of **8** was employed. The dihydroxylation of **8** was extremely slow and not observed when the reaction conditions described in the Experimental Section were employed. Unreacted **8** could be removed from the diol **7** during the isolation step.

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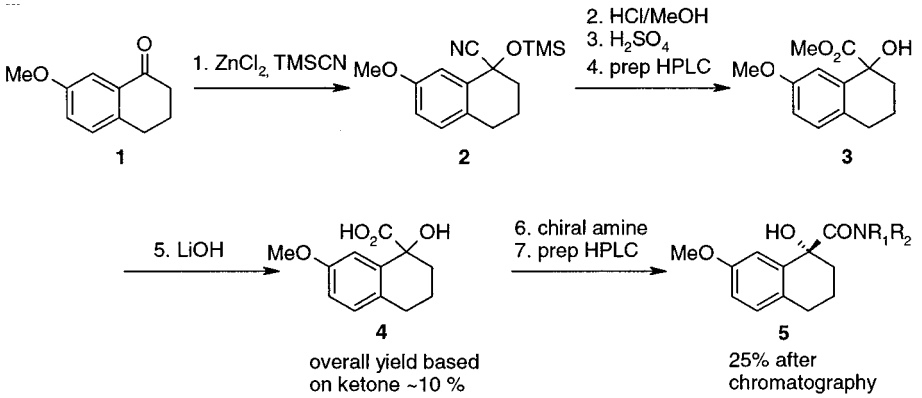
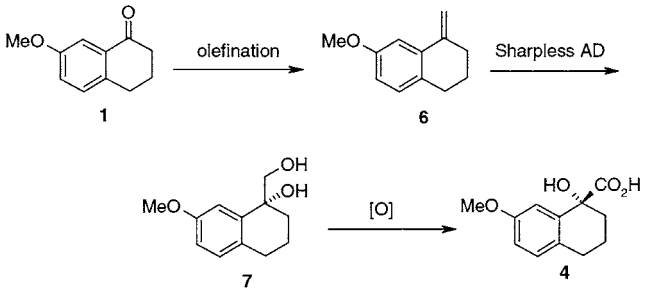
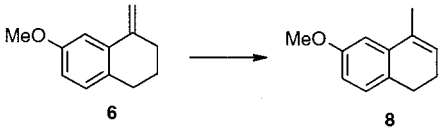
Scheme 1



Scheme 2



Scheme 3



that the obstacle preventing complete consumption of the starting material was the competing enolisation of the ketone. One minor improvement that resulted from these studies was the successful formation of the ylide at 0 °C, thereby circumventing the use of cryogenic equipment.

Replacing BuLi with ^{t}BuOK as a base[11] and addition of the latter (1 equiv) to a suspension of Ph_3PMeBr and **1** in THF at 0 °C gave an 84% conversion to **6**. Increasing the molar ratio of ylide to 1.5 equiv (wrt **1**) led to complete conversion. Out of the range of solvents evaluated (toluene, MTBE, THF and DME) that were employed in this reaction, THF was found to be the most appropriate.[12] Before scaling up the Wittig reaction, some optimisation was carried out. The volume of THF was reduced from 46 to 10 (wrt **1**) and ^{t}BuOK was introduced as a solution in THF to achieve a temperature-controlled addition.

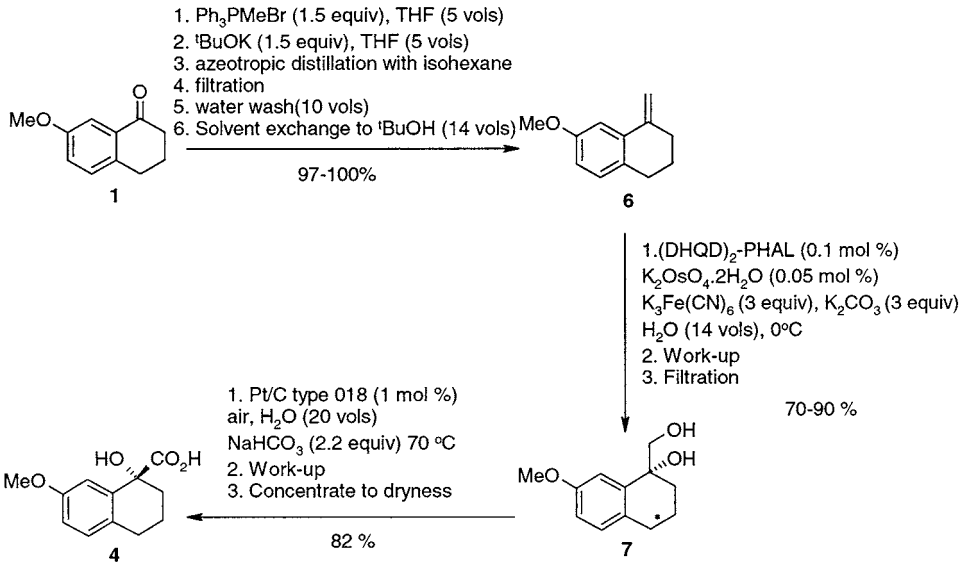
As discussed previously, chromatographic purification was required to isolate **6** of suitable quality. As conditions for the complete consumption of **1** had been identified, chromatography was carried out solely to remove triphenylphosphine oxide (TPPO) by-product. However, the large volumes of eluent required made this unviable, and an alternative procedure was sought. After completion of the reaction, THF was concentrated to a low volume and was replaced by isohexane by a series of azeotropic distillations.[13] Removal of THF was essential to prevent significant contamination of isolated product **6** with TPPO. During the azeotropic distillations, no isomerisation to alkene **8** was observed (NMR, HPLC). The suspension was filtered and washed with water. The resulting isohexane solution could be concentrated in vacuo to give **6** as an oil. Alternatively, a second solvent exchange to ^{t}BuOH gave a solution of **6** that could be used in the next step.

In parallel with our investigation into the Wittig reaction we also examined other olefination reactions. Employing the conditions described by Lombardo,[14] for the formation of alkenes using a titanium reagent prepared from $TiCl_4$, gave only trace amounts of the exomethylene compound **6**. Replacement of $TiCl_4$ with Cp_2ZrCl_2 gave **6** in a meagre 17% yield.[15] Peterson olefination using (trimethylsilylmethyl) Li, Mg, or Ce organometallic reagents[16] also resulted in incomplete consumption of **1**. The use of boron trifluoride etherate as the Lewis acid in these reactions gave a low (<10% of **6**), but direct, conversion of **1** to **6** (via the β-hydroxysilane). Horner-Emmons olefination was also investigated. The addition of dimethyl methylphosphonate and BuLi to **1** was optimised to give 88% yield of the β-hydroxy phosphonate in high purity. However, elimination of the β-hydroxy phosphonate to give the olefin **6** proved problematic. Standard conditions[17] gave significant amounts of **1** from the retro-reaction. Optimisation of the elimination reaction in order to minimise the formation of **1**, gave improved yields of **6**; however, work was concluded at this point due to the greater efficiency and ease of operation of the Wittig reaction.

The Wittig reaction has been carried out several times on a 200-g scale (wrt **1**) using the conditions shown in Scheme 4. The reaction was complete after all of the base had been added. Work-up and purification as above provided **6** in 97−100% isolated yield, in 95−99.7% purity (HPLC) contaminated by only 0.3−1.64% TPPO (**8** was not detected), that was acceptable in the next step.[18]

(11) Ohta, T.; Ikegami, H.; Miyake, T.; Takaya, H. *J. Organomet. Chem.* **1995**, *502*, 169.
(12) THF gave the best results in terms of yield and purity. Higher-boiling solvents (toluene and DME) led to isomerisation of the product (Scheme 3). A lower yield was obtained when MTBE was used as the solvent.
(13) For other examples of use of a hydrocarbon solvent in a Wittig work-up see Pommer, H. *Pure Appl. Chem.* **1975**, *43*, 527.
(14) Lombardo, L. *Tetrahedron Lett.* **1982**, *23*, 4293.
(15) Hartmann, M.; Zbiral, E. *Liebigs Ann. Chem.* **1991**, 795.
(16) Johnson, C.R.; Tait, B. D. *J. Org. Chem.* **1987**, *52*, 169.
(17) Kwiatowski, G.T.; Corey, E. J. *J. Am. Chem. Soc.* **1966**, 5654. Kawashima, T.; Ishii, T.; Inamoto, N. *Chem. Lett.* **1984**, 1097.

Scheme 4



Sharpless Asymmetric Dihydroxylation (AD). Initial conditions[19] for the dihydroxylation of **6**: $(DHDQ)_2PHAL$ (1 mol %), $K_2OsO_4{\cdot}2H_2O$ (0.5 mol %), $K_3Fe(CN)_6$ (3 equiv) and K_2CO_3 (3 equiv) in ^{t}BuOH (30 vols):H_2O (30 vols) at 0 °C for 16 h gave, after work-up and concentration of the ethyl acetate solution in vacuo, **7** as a white solid in 93% yield. Using $(DHQ)_2PHAL$ as the ligand, the enantiomer of **7** was similarly prepared. Chiral HPLC showed the diol **7** was typically prepared in 98−99.8% ee.

Prior to scale-up of the dihydroxylation reaction[20] some optimisation was carried out. The quantity of ^{t}BuOH and H_2O was reduced from 60 vols (wrt alkene **6**) to 28 vols in total. (Further reduction of the reaction volume was not possible as the reagents were no longer fully solublised.) The reaction was carried out successfully at 20−25 °C, leading to improved rates of reaction (3 h) without affecting the ee of product **7**. The quantities of osmate catalyst and $(DHQD)_2PHAL$ were reduced by a factor of 10 to 0.05 and 0.1 mol % respectively. IPA and MTBE were investigated as alternatives to ^{t}BuOH. Reaction in IPA proceeded as usual but gave diol **7** in lower ee (96% by chiral HPLC). In MTBE, the reaction was much slower and complete consumption of starting materials took 5 days.

The isolation procedure was additionally improved for the scale-up process. EtOAc could be replaced with ^{i}PrOAc (less likely to hydrolyse in acid wash and greater partition coefficient with H_2O) in the work-up. On completion of the required washes, the organic layer was concentrated, and isohexane was added, leading to precipitation of diol **7**. The latter was then isolated by filtration. Further optimisation of the isolation procedure was not possible due to time constraints.

A 100-g (wrt **6**)-scale reaction was carried out using the optimised conditions. Crystallisation of **7** using EtOAc/isohexane gave a 71% recovery of **7**.

Oxidation. With a suitable synthesis of **7** in place we then turned our attention to the oxidation reaction. Various conditions were examined for the direct conversion of the primary alcohol to carboxylic acid **4**.[21] Air-mediated oxidation using a Pt/C catalyst[22] gave a clean conversion of **7** to **4**. Using the conditions described by Sharpless (with the omission of Dow Corning Antifoam A),[23] several catalyst types (Johnson Matthey type 117, 128, and 018) were investigated. Type 018 (eggshell, Pt distributed on the surface) afforded an 86% yield of **4** in 18 h and was therefore selected as the catalyst of choice.

In initial reactions using the Sharpless conditions, 100 vols of H_2O (wrt **7**) and 5 mol % of catalyst were employed. Reduction in the H_2O volume also led to slower rates of reaction; 20 vols of water (wrt **7**) gave a reaction time of 48 h. Further reduction to 10 vols of H_2O resulted in some precipitation of **7**. The catalyst loading could be reduced to 1 mol % without affecting the rate. Although 48 h is a significantly long reaction time, it should be noted that the reaction was carried out using standard laboratory glassware, and it was anticipated that more specialised equipment for solid−liquid-gas mixing (i.e. Buss-Loop reactor) and perhaps the use of high pressures would overcome this in the longer term. However, at this stage in our development program these reaction times were acceptable.

The oxidation has been carried out on scales up to 16 g (wrt **7**) using 1 mol % Pt/C and 20 vols of H_2O. The reactions were complete after 48 h. Work-up[24] gave **4** in 80−85% yield and 98−99.8% ee and levels of Os and Pt below the limits of detection (<5 ppm, ICP-AES).

In summary, we have developed a short, efficient synthesis of **4** from **6** that does not rely on chromatography and was capable of providing sufficient quantities of **4** in

(18) Alkene **6** contaminated with 10% TPPO was tolerated in the Sharpless dihydroxylation reaction.
(19) Vanhessche, K. P. M.; Sharpless, K. B. *J. Org. Chem.* **1996**, *61*, 7978.
(20) For an example of a Sharpless asymmetric dihydroxylation on an industrial scale see Ahrgren, L.; Sutin, L. *Org. Process Res. Dev.* **1997**, *1*, 425.
(21) We chose to focus on the direct conversion rather than the two-step transformation via the aldehyde.
(22) Heyns, K.; Blazejewicz, L. *Tetrahedron* **1960**, *9*, 67.
(23) Bennani, Y.L.; Vanhessche, K. P. M.; Sharpless, K. B. *Tetrahedron Asymmetry* **1994**, *5*, 1473.
(24) The carboxylic acid was isolated as an oil. Further development planned includes investigation into the formation of a suitable crystalline salt.

acceptable quality to assist in our development program. Further work on scale-up was planned, but work was halted at this stage, as it was decided not to progress the drug candidate further.

Experimental Section

General. All starting materials and key reagents were purchased from Aldrich or Fluka and used without further purification unless otherwise stated. The HPLC method for reaction monitoring and ee determination can be found in the Supporting Information. ^{1}H NMR spectra were recorded on a Varian 300 or 400 MHz instrument. Chemical shifts for ^{1}H NMR are reported in ppm downfield relative to TMS as an internal standard in $CDCl_3$.

Wittig Olefination. To a nitrogen-inerted round-bottom flange flask equipped with an overhead stirrer, a solution of potassium *tert*-butoxide (208.07 g, 1.702 mol, 1.5 equiv) in THF (1.04 L) was added to a suspension of ketone **1** (200 g, 1.135 mol) and Ph_3PMeBr (611.6 g, 1.702 mol, 1.5 equiv) in THF (1 L) at ambient temperature over 1 h, maintaining a temperature below 50 °C. HPLC analysis showed that the reaction was complete at the end of addition. THF (ca 1.5 L) was removed by distillation, followed by the addition of isohexane (1.5 L). The distillation was continued, and a further volume of THF was removed (ca. 1.8 L). Isohexane (2 L) was added, and the slurry was stirred for 1 h at ambient. The slurry was filtered, and the organic layer was washed with water (2 L) and concentrated to give the alkene **6** as an oil (195.8 g, 1.124 mol, 99%). Alternatively, a solvent exchange (^{t}BuOH/isohexane) gave the product in solution for the next step. ^{1}H NMR ($CDCl_3$) 1.82−1.90 (2H, m), 2.48−2.57 (2H, m), 2.78 (2H, t, *J* 6.3 Hz), 3.81 (3H, s), 4.96 (1H, d, *J* 0.8 Hz), 5.45 (1H, d, *J* 0.8 Hz), 6.77 (1H, dd, *J* 2.8 and 8.5 Hz), 7.00 (1H, d, *J* 8.5 Hz), 7.16 (1H, d, *J* 2.6 Hz). LCMS (*m*/*z*): 174 (M + 1). IR (cm^{-1}) 1490, 1234, 1037, 867.

Sharpless AD. A solution of alkene **6** (100 g, 574 mmol) in ^{t}BuOH (1.44 L) was added to K_2CO_3 (238 g, 1722 mmol, 3 equiv), $K_3Fe(CN)_6$ (567 g, 1722 mmol, 3 equiv), $K_2OsO_2(OH)_4$ (0.11 g, 0.29 mmol, 0.05 mol %), and $(DHQD)_2$−PHAL (0.45 g, 0.57 mmol, 0.1 mol %) in water (1.44 L), in a round-bottom flange flask equipped with an overhead stirrer at ambient temperature. After HPLC analysis showed that the reaction was complete, an aqueous solution of $Na_2S_2O_5$ (574 g in 1.15 L of H_2O) was added dropwise. The mixture was stirred for a further 2 h at ambient temperature (alternatively, the mixture could be stirred overnight). EtOAc (1.44 L) was added, and the two layers were separated. The organic layer was washed sequentially with H_2O (861 mL), 2 M H_2SO_4 (574 mL), $NaHCO_3$ (861 mL), and brine (861 mL). The organic phase was concentrated to 5% of the original volume, and isohexane (2 L) was added. The product precipitated and was collected by filtration. The solid was washed with isohexane (2 × 250 mL) and dried on the Buchner funnel for 1 h at ambient temperature. Yield of diol **7** = 85.3 g (71%). Mp = 92−94 °C. ^{1}H NMR ($CDCl_3$) 1.67−1.96 (2H, m), 2.04−2.34 (2H, m), 2.21 (1H, s), 2.74 (2H, dt, *J* 8.9 and 5.6 Hz), 3.61−3.74 (2H, m), 3.80 (3H, s), 6.78 (1H, dd, *J* 2.8 and 8.5 Hz), 7.02 (1H, d, *J* 8.5 Hz), 7.09 (1H, d, *J* 2.6 Hz). LCMS (*m*/*z*): 209 (M + 1). IR (cm^{-1}) 3291, 1237, 1039. $[\alpha]^{25}_D = -30.35°$ (*c* = 0.59, MeOH).

Pt/C Oxidation. Diol **7** (7.8 g, 37.5 mmol), 5% Pt/C (JM 018, 3.6 g, 58.5% H_2O, 1 mol %) and $NaHCO_3$ (6.9 g, 82.4 mmol, 2.2 equiv) were slurried in water (156 mL) at 70 °C, and air was bubbled through the slurry. After 48 h, HPLC analysis indicated that the reaction was complete. The reaction was cooled to ambient temperature and filtered through a small pad of Celite. The resulting aqueous solution was acidified with 2 M H_2SO_4 to pH 2 and then extracted into EtOAc (2 × 230 mL). The combined organic extracts were concentrated in vacuo to give the product **4**, as an amber oil. ^{1}H NMR ($CDCl_3$) 1.85−2.22 (3H, m), 2.24−2.32 (1H, m), 2.69−2.83 (2H, m), 3.76 (3H, s), 6.77 (1H, d, *J* 2.5 Hz), 6.82 (1H, dd, *J* 2.5 & 8.5 Hz), 7.06 (1H, d, *J* 8.5 Hz). LCMS (*m*/*z*) 221 (M − 1).

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Supporting Information Available

HPLC methods. This material is available free of charge via the Internet at http://pubs.acs.org.

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