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Supplementary Material Available: A summary table of the results of the benzannulation reaction study (eqs 1-2), full experimental for **2**, **8-9**, **20**, **54-64**, characterization of **26**, **28-31**, **33**, **39-40**, **42-43**, and **45**, and ^{1}H NMR spectra of **12**, **33**, **65c**, **70**, **74**, and **75** (24 pages). Ordering information is given on any current masthead page.

Efficient Oxidation of Phenyl Groups to Carboxylic Acids with Ruthenium Tetraoxide. A Simple Synthesis of (*R*)-γ-Caprolactone, the Pheromone of *Trogoderma granarium*

M. Teresa Nuñez and Victor S. Martín*

Centro de Productos Naturales Orgánicos "Antonio González", Instituto Universitario de Bio-Orgánica, Universidad de La Laguna, 38206 La Laguna, Tenerife, Spain

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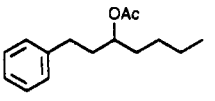
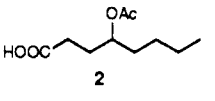
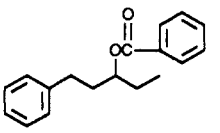
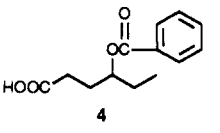
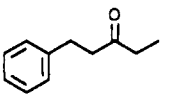
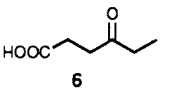
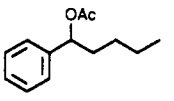
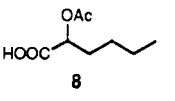
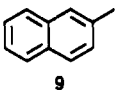
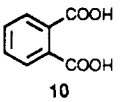
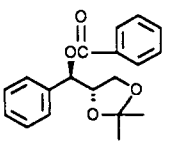
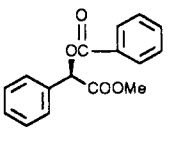
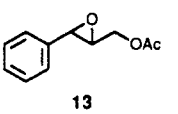
The oxidation of aromatic rings to carboxylic acids with ruthenium tetraoxide is shown to be a very efficient and simple reaction using periodic acid as the stoichiometric oxidant in a biphasic solvent system (CCl_4, CH_3CN, H_2O). The reaction can be very sensitive to the nature of the ring substituents when more than one aromatic ring is present. The procedure is compatible with other functional groups except for those that are quite acid sensitive. A simple synthesis of (*R*)-γ-caprolactone employs Sharpless asymmetric epoxidation and the presented oxidation procedure as key steps.

The utility of ruthenium tetraoxide as an organic oxidant has been widely recognized.[1] Catalytic procedures using stoichiometric oxidants such as periodate,[1,2] hypochlorite,[1,3] bromate,[4] permanganate,[4] cerium sulfate,[4] and electrochemically generated $Cl_2[Cl^+]$[5] have been reported. In 1981, Sharpless et al.[6] reported an improved procedure to oxidize a wide range of organic functions based on the use of a biphasic system containing acetonitrile, as a special additive to prevent catalyst inactivation, and sodium periodate as the stoichiometric oxidant. This method has since become almost a standard procedure for the oxidative cleavage of olefins,[7] diols,[8] cyclic allylic alcohols, and α,β-unsaturated ketones[9] and oxidation of primary alcohols to carboxylic acid,[10] ethers to esters,[11] acetylenes to 1,2-diketones,[12] furan[13,14] and thiophene[13] rings to carboxylic acids, and cyclic sulfites to cyclic sulfates.[15]

Table I

compd	product	yield, %
 1	 2	76
 3	 4	80
 5	 6	65
 7	 8	60
 9	 10	62
 11	 12	84[a]
 13	irresolvable mixture	

[a] Isolated as methyl ester.

Although two cases of oxidation of an aromatic ring to a carboxylic acid, with good yields, are reported in the

(1) (a) Lee, D. G.; van der Engh, M. In *Oxidation in Organic Chemistry*; Trahanovsky, W. S., Ed.; Academic Press: New York, 1973; Part B, Chapter 4. (b) Gore, E. S. *Platinum Met. Rev.* **1983**, *27*, 111.
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0022-3263/90/1955-1928$02.50/0

above-mentioned paper[6] and the procedure has been used in synthetic work,[13,16] it needs modification of the concentration conditions, and when the reaction is run on more than a 1–2-mmol scale, serious problems appear which prevent the reaction from reaching completion. In such cases, the removal of the precipitated sodium iodate is required and the reaction is run once again to completion.

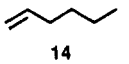
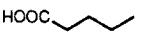
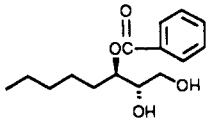
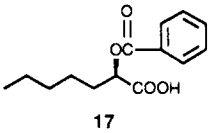
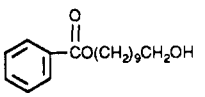
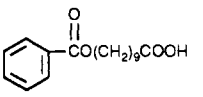
On the other hand, periodic acid has been suggested as an alternative to sodium periodate in all ruthenium oxidations, even for aromatic rings.[17] However, no systematic studies about its use as a stoichiometric oxidant have been published to date. In this paper, we report that such a simple change overcomes all the above-mentioned problems for aromatic ring oxidations, even under "normal" concentration conditions (2 mL of CH_3CN–2mL of CCl_4–3 mL of H_2O/mmol of aromatic compound) and in larger scale reactions (up to 50 mmol). A typical procedure is almost identical with that reported for sodium periodate,[6] normal periods of reaction time being 2–3 h, and reaction temperature simply being controlled within the range 25–40 °C with a combination of stirring and in some cases a cooling bath. At temperatures below 20 °C, the reaction almost stops, and above 40 °C, it becomes uncontrollable due to overheating, with a high risk of the reaction spilling over. In small-scale procedures (e.g., less than 3 mmol), no temperature control is necessary when the reaction is carried out in an open flask to avoid pressurization because of the CO_2 generated.

We have tested the procedure in a few cases (Table I) and found that the phenyl group may be a useful synthetic equivalent of the carboxylic acid group, mainly on the basis of the fact that aromatic rings present an extraordinary stability to a great number of reagents, with the exception, of course, of those that are strongly electrophilic or strongly reducing. Thus, a combination of the nucleophilic use of aryl Grignard, aryllithium, lithium diarylcuprates, etc., with convenient electrophilic reagents such as alkyl halides or arenesulfonates, saturated and unsaturated carbonyl compounds, etc., may provide a useful route to the carboxylic acid functionality. Another interesting feature of this aromatic oxidation is that very high chemoselectivity can be achieved when more than one aromatic ring is present, depending only on the nature of the ring substituents. Thus, in compounds **3** and **9** (Table I), selective oxidation of the more activated ring can be performed with high chemoselectivity. This electron-withdrawing substituent effect has also been described by Ziffer et al. in the ruthenium oxidation of aromatic compounds using $NaIO_4$ as the stoichiometric oxidant.[13]

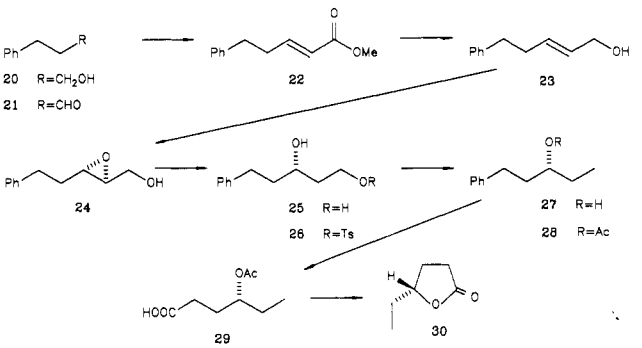
As can be observed in compounds **11** and **13** (Table I), the procedure is not useful when acid-sensitive groups are present, because these are attacked first and oxidation of the released functionality is the main side reaction. In these cases, sodium periodate continues to be the best choice as the stoichiometric oxidant.

The use of periodic acid as a stoichiometric oxidant is also very convenient in the oxidation of primary alcohols, alkenes, or diols to carboxylic acid (Table II), with similar yields to those obtained with sodium periodate by following the standard experimental procedure[6] but with an easier isolation step.

Table II

compd	product	yield, %
 **14**	 **15**	80
 **16**	 **17**	91
 **18**	 **19**	84

Scheme I



To test how the procedure can be used for the synthesis of natural products, we describe the enantioselective total synthesis of (*R*)-γ-caprolactone (**30**), the insect pheromone of *Trogoderma granarium*[18] (Scheme I). Commercially available 3-phenyl-1-propanol (**20**) was oxidized with pyridinium chlorochromate[19] in dichloromethane at room temperature and, without any purification, was treated with the sodium salt of trimethyl phosphonoacetate [$Na^+(MeO)_2P(O)CH^-COOMe$], giving rise to the unsaturated ester **22**. The reduction of **22** was carried out with $LiAlH_4/AlCl_3$ in ether, yielding the (*E*)-allylic alcohol **23**, which was submitted to asymmetric epoxidation[20] using L-(+)-diethyl tartrate [L-(+)-DET] as chiral auxiliary, to afford the 2,3-epoxy alcohol **24** with greater than 95% enantiomeric excess.[21] The reduction of **24** with Red-Al (Aldrich) in THF[22] yielded almost exclusively the 1,3-diol **25** (greater than 100:1, checked by ^1H NMR of the corresponding diacetates). Monotosylation of **25** and reduction, without purification, with lithium aluminum hydride in THF led to the chiral alcohol **27**, which was acetylated under standard conditions. The acetate **28** was oxidized under the general conditions reported in this paper, affording the acid **29** (72% yield), which after saponification and further acid treatment yielded the (*R*)-γ-caprolactone

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(17) Footnote 23 in ref 8b; footnote 4 in ref 10. The superiority of periodic acid over sodium periodate in RuO_4 oxidations of aromatic compounds has been previously indicated by Kwok Tse and Professor Leon Stock of the University of Chicago: Stock, L. M.; Tse, K. W.-T. *Fuel* **1983**, *62*, 974.
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(30) $[\alpha]_D^{25}$ +50.8° (c 1.3, MeOH) [lit.[23] $[\alpha]_D^{20}$ +53.2° (c 1.0, MeOH)].[24]

In summary, we believe that periodic acid is clearly the best choice as the stoichiometric oxidant in all ruthenium oxidations,[25] with the exception of those cases where acid-sensitive groups are present.

Experimental Section

Materials and Methods. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker WP 200SY spectrometer in $CDCl_3$ as solvent, and chemical shifts are reported relative to Me_4Si. Low- and high-resolution mass spectra were obtained from a VG Micromass ZAB-2F spectrometer. Optical rotations were determined for solutions in chloroform or ethanol with a Perkin-Elmer Model 241 polarimeter. Infrared spectra were recorded on a Perkin-Elmer Model 402 spectrophotometer. GC analyses were performed on a Hewlett-Packard HP5790-A instrument with a capillary column, OV-1, 25 m. Column chromatography was performed on silica gel, 0.005–0.2 mm, and TLC and PLC were performed on silica gel, all Merck products. Visualization of spots was effected with UV light and/or phosphomolybdic acid in ethanol stain. All solvents were purified by standard techniques. Reactions requiring anhydrous conditions were performed under argon. Anhydrous magnesium sulfate was used for drying solutions.

General Procedure for Phenyl Group Oxidations. Oxidation of 1-Phenyl-3-heptanol Acetate (1) to 4-(Acetyloxy)octanoic Acid (2). Large Scale. (This is considered to be when more than 3 mmol of aromatic compound is to be oxidized.) A 0.5-L, three-necked, round-bottomed flask equipped with a Teflon-covered magnetic stirring bar, thermometer, septum, and wide-bore gas outlet (because of the generation of carbon dioxide, it is very important to use this to avoid overpressure) was charged with **1** (11.7 g, 50 mmol), carbon tetrachloride (100 mL), acetonitrtile (100 mL), water (150 mL), and periodic acid (162 g, 710 mmol, 14.2 equiv). The flask contents were stirred until both phases became clear. To the flask added ruthenium trichloride hydrate (250 mg, 0.02 equiv), and the reaction mixture was stirred, the temperature being kept within the temperature range of 25–40 °C by control of the stirring speed and, as needed, with an ice–water cooling bath, until no aromatic compound was detected by TLC or GLC (a normal period of reaction time is about 2–3 h, mainly depending on stirring rate and reaction temperature). The reaction mixture was cooled to 0 °C with an ice bath, and ether (200 mL) was added (a deep black color appeared at this point) with vigorous stirring for 10 min. The flask contents were transferred to a 1-L separatory funnel. The organic phase was separated and the aqueous layer extracted with ether (2 × 100 mL). The combined organic layers were washed with brine (2 × 100 mL), dried, filtered, and concentrated. The crude product was purified by bulb-to-bulb distillation (bp_{5mm} 240–250 °C), affording 7.6 g (76%) of **2** as a yellow oil. GC analysis showed a chemical purity of 98%: ^1H NMR δ 0.89 (t, J = 7.0 Hz, 3 H), 1.36 (m, 4 H), 2.07 (s, 3 H), 2.48 (m, 2 H), 2.48 (m, 1 H); ^{13}C NMR δ 13.85 (q), 22.37 (q), 27.30 (t), 27.96 (t), 28.83 (t), 35.20 (t), 81.08 (d), 177.40 (s); IR ($CHCl_3$) (cm^{-1}) 3490, 3000, 2940, 2830, 1740, 1450, 1330, 1180, 1010, 890; MS m/z (relative intensity) 202 (1), 143 (3), 85 (100); HRMS calcd for $C_{10}H_{18}O_4$ 202.1205, obsd 202.1229.

Small Scale. (This is considered to be when less than 3 mmol of aromatic compound is to be oxidized.) The procedure is identical with that described above for the large scale with the exception of the temperature control, which is unnecessary (room temperature). In any case, the reaction must be carried out in an open flask or one equipped with a wide-bore gas outlet to avoid pressurization by the CO_2 generated.

Oxidation of 5-Phenyl-3-(benzoyloxy)pentane (3) to 4-(Benzoyloxy)hexanoic Acid (4). The general procedure (large scale) was used to oxidize **3** (916 mg, 3.42 mmol) in 3 h, yielding, after bulb-to-bulb distillation, **4** (670 mg, 83% yield): ^1H NMR δ 0.98 (t, J = 7.5 Hz, 3 H), 1.75 (m, 2 H), 2.05 (m, 2 H), 2.45 (t, J = 7.5 Hz, 2 H), 5.12 (m, 1 H), 7.5 (m, 3 H), 8.1 (m, 2 H); ^{13}C NMR δ 9.71 (q), 27.26 (t), 28.72 (t), 30.25 (t), 75.18 (d), 126.02 (s), 128.52 (d), 129.73 (d), 132.96 (s), 133.10 (d), 179.03 (s); IR ($CHCl_3$) (cm^{-1}) 3400, 3020, 2940, 1710, 1310, 1250, 1100, 880; MS m/z (relative intensity) 236 (1), 146 (29), 117 (43), 105 (100), 104 (25), 91 (28), 77 (79); HRMS calcd for $C_{13}H_{16}O_4$ 236.1049, obsd 236.1053.

Oxidation of 5-Phenyl-3-pentanone (5) to 4-Oxohexanoic Acid (6). The general procedure (small scale) was used to oxidize **5** (3.44 mg, 2.12 mmol) in 2.45 h, yielding, after bulb-to-bulb distillation, **6** (179 mg, 65% yield): mp 33–35 °C (lit.[26] mp 34–35 °C); ^1H NMR δ 1.07 (t, J = 7.0 Hz, 3 H), 2.45 (m, 2 H), 2.67 (m, 4 H); ^{13}C NMR δ 7.88 (q), 27.99 (t), 35.98 nt), 36.51 (t), 1768.68 (s); IR (film) (cm^{-1}) 3390, 3020, 2960, 1700, 1410, 1110; MS m/z (relative intensity) 130 (2), 101 (71), 73 (35), 57 (100); HRMS calcd for $C_6H_{10}O_3$ 130.0630, obsd 130.0617.

Oxidation of 1-Phenyl-1-(acetyloxy)pentane (7) to 2-(Acetyloxy)hexanoic Acid (8). The general procedure (small scale) was used to oxidize **7** (152 mg, 0.73 mmol) in 2 h, yielding, after bulb-to-bulb distillation, **8** (83 mg, 65%): ^1H NMR δ 0.90 (t, J = 7.0 Hz, 3 H), 1.37 (m, 4 H), 1.85 (m, 2 H), 2.02 (s, 3 H), 4.99 (t, J = 6.0 Hz, 1 H), 8.19 (s, 1 H); ^{13}C NMR δ 13.92 (q), 20.72 (q), 22.37 (t), 27.33 (t), 30.79 (t), 72.19 (d), 176.00 (s); IR ($CHCl_3$) (cm^{-1}) 3390, 2990, 2940, 1730, 1310, 1030; MS m/z (relative intensity) 174 (1), 129 (87), 114 (11), 69(37), 55(100); HRMS calcd for $C_8H_{14}O_{14}$ 174.0892, obsd 174.0873.

Oxidation of 2-Methylnaphthalene (9) to *o*-Phthalic Acid (10). The general procedure (large scale) was used to oxidize **9** (0.5 g, 3.51 mmol) in 2.5 h, yielding, after chromatography and recrystallization, **10** (390 mg, 67% yield) [the obtained compound was compared with an authentic sample (Aldrich Chemical Company)]: mp 208–209 °C (lit.[27] mp 200–235 °C, depending on the heating rate); ^1H NMR (CD_3OD) δ 7.4 (m, 4 H); ^{13}C NMR (CD_3OD) δ 128.89 (d), 130.91 (d), 170.06 (s); IR ($CHCl_3$) (cm^{-1}) 3450, 2980, 1710, 1550; MS m/z (relative intensity) 166 (11), 149 (22), 122 (97), 105 (100), 77 (77), 76 (40); HRMS calcd for $C_8H_6O_4$ 166.0266, obsd 166.0245.

Oxidation of 4-[(*R*)-(Benzoyloxy)phenylmethyl]-2,2-dimethyl-1,3-dioxolane (11) to Methyl 1-Phenyl-1-(benzoyloxy)acetate (12). The general procedure (small scale) was used to oxidize **11**[8a] (686 mg, 2.2 mmol) in 1.5 h, yielding, after methyl ester formation (CH_2N_2, ether, room temperature, 10 min), **12** (493 mg, 83% yield): $[\alpha]^{25}_D$ −110.01° (c 1.5, $CHCl_3$); ^1H NMR δ 3.75 (s, 3 H), 6.18 (s, 1 H), 7.49 (m, 3 H), 8.12 (m, 2 H); ^{13}C NMR δ 52.77 (q), 74.97 (d), 127.75 (d), 128.56 (d), 128.99 (d), 129.41 (d), 130.10 (d), 133.60 (d); IR ($CHCl_3$) (cm^{-1}) 3010, 2990, 2910, 1740, 1710, 1440, 1240, 1100; MS m/z (relative intensity) 270 (1), 239 (1), 165 (2), 105 (100), 91 (4), 77 (79); HRMS calcd for $C_{16}H_{14}O_4$ 270.0892, obsd 270.0865.

Oxidation of 1-Hexene (14) to Pentanoic Acid (15). A flask was charged with CH_3CN (4.7 mL), CCl_4, (4.7 mL), H_2O (7.2 mL), 1-hexene (**14**, 200 mg, 2.3 mmol), and H_5IO_6 (2.15 g, 9.43 mmol). To this biphasic solution was added $RuCl_3 \cdot xH_2O$ (12 mg, 0.02 equiv), and the reaction mixture was vigorously stirred for 1.5 h at room temperature. To the reaction mixture was added ether (20 mL), and the stirring was continued for 10 min. The organic phase was separated, and the aqueous phase was extracted with ether (2 × 10 mL). The combined organic phases were washed with saturated brine, dried, and concentrated. The crude mixture was purified by bulb-to-bulb distillation, affording pentanoic acid (**15**, 188 mg, 80% yield): bp 180–190 °C (lit.[28] bp 185 °C); ^1H NMR δ 0.89 (t, J = 7.3 Hz, 3 H), 1.36 (m, 2 H), 1.57 (m, 2 H), 2.33 (t, J = 7.22, 2 H); ^{13}C NMR δ 13.71 (q), 22.24 (d), 26.81 (d), 33.87

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(d), 180.16 (s); IR ($CHCl_3$) (cm^{-1}) 3400, 3010, 2930, 2910, 1700; MS m/z (relative intensity) 102 (1), 101 (13), 87 (28), 83 (51), 73 (38), 60 (100); HRMS calcd for $C_5H_{10}O_2$ 102.0681, obsd 102.0697.

Oxidation of 3-(Benzoyloxy)-1,2-octanediol (16) to 2-(Benzoyloxy)heptanoic Acid (17). The same procedure used in the oxidation of **14** was used on a 4.68-mmol scale (1.246 g). After 1.5 h and chromatographic purification was obtained the acid **17** (1.06 g, 91%): ^1H NMR δ 0.90 (t, J = 6.7 Hz, 3 H), 1.34 (m, 4 H), 1.54 (m, 2 H), 2.15 (m, 2 H), 5.26 (t, J = 6.4 Hz, 1 H), 7.48 (m, 3 H), 8.06 (m, 2 H), 10.02 (s, 1 H); ^{13}C NMR δ 14.11 (q), 22.55 (t), 25.06 (t), 31.24 (t), 31.46 (t), 72.63 (d), 128.62 (d), 129.54 (s), 130.03 (d), 133.56 (d), 166.38 (s), 175.89 (s); IR ($CHCl_3$) (cm^{-1}) 3450, 3010, 2930, 2910, 2830, 1710, 1450, 1260, 1120; MS m/z (relative intensity) 250 (2), 133 (6), 145 (3), 128 (27), 105 (100), 77 (98); HRMS calcd for $C_{14}H_{18}O_4$ 250.1205, obsd 250.1194.

Oxidation of 1-(Benzoyloxy)-10-decanol (18) to 10-(Benzoyloxy)decanoic Acid (19). The same procedure for the oxidation of **14** was used on a 0.61-mmol scale (170 mg). After 1.5 h and chromatographic purification was obtained the acid **19** (149 mg, 84% yield): ^1H NMR δ 1.31 (m, 10 H), 1.65 (m, 4 H), 2.33 (t, J = 7.4 Hz, 2 H), 4.30 (t, J = 6.5 Hz, 2 H), 7.46 (m, 3 H), 8.02 (m, 2 H); ^{13}C NMR δ 24.75 (t), 26.09 (t), 28.78 (t), 29.09 (t), 29.23 (t) 29.27 (t), 29.37 (t), 34.20 (t), 65.22 (t), 128.41 (d), 129.63 (d), 132.90 (d), 166.83 (s), 180.21 (s); IR ($CHCl_3$) (cm^{-1}) 3500, 3040, 2960, 2880, 1730, 1460, 1310, 1140; MS m/z (relative intensity) 292 (1), 152 (18), 123 (88), 122 (20), 105 (100), 98 (23), 77 (95); HRMS calcd for $C_{17}H_{24}O_4$ 292.1675, obsd 292.1672.

Methyl (2*E*)-5-Phenyl-2-pentenoate (22). To a suspension of pyridinium chlorochromate (7.13 g, 33.1 mmol) in CH_2Cl_2 (100 mL) containing crushed activated 3-Å molecular sieves (3.0 g), at 0 °C, was added dropwise 3-phenyl-1-propanol (**20**, 3 g, 22.1 mmol) dissolved in CH_2Cl_2 (10 mL), and the mixture was stirred until no alcohol was detected by TLC (3 h). Ether (300 mL) was added, and the mixture was stirred for 10 min. The mixture was filtered through a bed of Florisil and washed with ether (3 × 20 mL). The resulting solution was concentrated, yielding a dark oil of the crude aldehyde **21**, which was used without purification.

To a suspension of sodium hydride [1.31 g (80% in mineral oil), 44.12 mmol] in benzene (400 mL), at 0 °C, was added slowly $(MeO)_2P(O)CH_2COOMe$ (7.5 mL, 46.3 mmol). After complete addition, the mixture was stirred for 5 min and the crude aldehyde **21** dissolved in benzene (10 mL) was added dropwise. The reaction mixture was stirred for 30 min, after which time TLC showed complete conversion to the unsaturated ester **22**. To the reaction mixture was added water (200 mL), and the aqueous layer was extracted with ether (2 × 50 mL). The organic layers were combined and dried, and the solvent was evaporated. The reaction mixture was chromatographed on a silica gel column, to yield **22** (3.19 g, 76% yield): ^1H NMR δ 2.50 (m, 2 H), 2.77 (t, J = 7.1 Hz, 2 H), 3.71 (s, 3 H), 5.85 (d, 1 H), 7.15 (m, 1 H), 7.27 (m, 5 H); ^{13}C NMR δ 33.98 (t), 34.45 (t), 51.50 (q), 121.60 (d), 126.29 (d), 128.44 (d), 128.60 (d), 148.30 (d), 167.06 (s); IR ($CHCl_3$) (cm^{-1}) 2980, 2900, 1710, 1650, 1380; MS m/z (relative intensity) 190 (1), 159 (2), 131 (3), 118 (70), 91 (100); HRMS calcd for $C_{12}H_{14}O_2$ 190.0994, obsd 190.0984.

(2*E*)-5-Phenyl-2-penten-1-ol (23). To a suspension of $LiAlH_4$ (716 mg, 18.8 mmol) in ether (170 mL) at 0 °C was added $AlCl_3$ (837 mg, 6.3 mmol) slowly. The mixture was stirred for 5 min, and the ester **22** (3.18 g, 16.7 mmol) dissolved in ether (10 mL) was added dropwise. The reaction mixture was stirred for 0.5 h, at which time TLC showed complete conversion. HCl (5%) in water (50 mL) was added, with stirring, until clear phases were obtained (15 min). The organic phase was separated, and the aqueous phase was extracted with ether (2 × 25 mL). The combined organic phases were washed with a saturated solution of $NaHCO_3$ and saturated brine and dried, and the solvent was evaporated, to yield, after chromatographic separation, **23** (2.46 g, 91% yield): ^1H NMR δ 2.38 (m, 2 H), 2.71 (m, 2 H), 4.05 (m, 2 H), 5.68 (m, 2 H), 7.25 (m, 5 H); ^{13}C NMR δ 34.33 (t), 35.65 (t), 63.76 (t), 125.99 (d), 128.45 (d), 128.55 (d), 179.75 (d), 132.33 (d), 141.82 (s); IR ($CHCl_3$) (cm^{-1}) 3540, 3400, 3000, 2910, 2830, 1490, 1450, 960; MS m/z (relative intensity) 162 (1), 144 (18), 129 (11), 91 (100), 65 (20); HRMS calcd for $C_{11}H_{14}O$ 162.1045, obsd 162.1042.

(2*S*-*trans*)-3-(2-Phenylethyl)oxirane Methanol (24). Powdered activated molecular sieves (4 Å, 0.5 g) were added to stirred CH_2Cl_2 (170 mL). The flask was cooled to −20 °C, and $Ti(O\text{-}i\text{-}Pr)_4$ (4.85 mL, 18.4 mmol), L-(+)-DET (3.04 mL, 20.1 mmol), and the allylic alcohol **23** (2.40 g, 14.8 mmol) were added sequentially with stirring. The reaction mixture was stirred for 20 min, and TBHP (6.30 mL, 4.5 M in isooctane, 29.6 mmol) was added slowly. After the addition, the reaction was maintained with stirring for 3 h. Tartaric acid aqueous solution (15%, 100 mL) was added, and the stirring was continued until clear phases were reached (30 min). The phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic phases were concentrated, diluted with ether (100 mL), and treated with a precooled (0 °C) solution of 15% NaOH (w/v) in saturated brine (30 mL). The two-phase mixture was stirred vigorously for 1 h at 0 °C. After phase separation, the aqueous phase was extracted with ether (2 × 50 mL). The reaction mixture was dried, evaporated, and chromatographed on a silica gel column, to yield **24** (2.29 g, 87% yield, >95% ee by ^1H NMR analysis of the Mosher's ester):[19] $[\alpha]^{25}_D$ −32.4° (*c* 1.98, $CHCl_3$); ^1H NMR δ 1.87 (m, 2 H), 2.75 (m, 2 H), 2.99 (m, 2 H), 5.65 (m, 1 H), 3.85 (m, 1 H), 7.25 (m, 5 H); ^{13}C NMR δ 32.19 (t), 33.35 (t), 55.48 (d), 58.90 (d), 61.76 (t), 126.14 (d), 128.40 (d), 129.49 (d); IR ($CHCl_3$) (cm^{-1}) 3400, 2980, 2900, 1430, 1220, 1075; MS m/z (relative intensity) 178 (1), 161 (2), 143 (40), 129 (32), 91 (100); HRMS calcd for $C_{11}H_{14}O_2$ 178.0994, obsd 178.0980.

(3*S*)-5-Phenyl-1,3-pentanediol (25). To a cooled solution (−20 °C) of **24** (2.26 g, 12.7 mmol) in THF (120 mL) was slowly added Red-Al (4.48 mL, 3.4 M in toluene, 15.2 mmol). The reaction mixture was monitored by TLC until no epoxide was visible (3 h). Then water (10 mL) and 5% HCl in water (25 mL) were added sequentially to quench the reaction, and stirring was continued until clear phases were reached (0.5 h). The organic phase was separated and the aqueous phase extracted with ether (3 × 15 mL). The combined organic solutions were washed with saturated aqueous $NaHCO_3$ (2 × 15 mL) and saturated brine (15 mL), dried, and concentrated. Purification by column chromatography gave **25** (1.71 g, 75% yield): $[\alpha]^{25}_D$ −7.21° (*c* 1.52, EtOH); ^1H NMR δ 1.81 (m, 2 H), 2.75 (m, 4 H), 4.91 (m, 3 H), 7.25 (m, 5 H); ^{13}C NMR δ 32.03 (t), 38.50 (t), 39.47 (t), 61.86 (t), 71.66 (d), 126.02 (d), 128.55 (d); IR ($CHCl_3$) (cm^{-1}) 3980, 3075, 3040, 1080; MS m/z (relative intensity) 178 (1), 162 (30), 144 (15), 129 (42), 91 (100); HRMS calcd for $C_{11}H_{16}O_2$ 180.1150, obsd 180.1113.

(3*R*)-1-Phenyl-3-pentanol (27). To a stirred solution of diol **25** (1.7 g, 9.45 mmol) in dry pyridine (30 mL) was added freshly purified *p*-toluenesulfonyl chloride (1.9 g, 9.98 mmol) at 0 °C. The reaction mixture was stored in a refrigerator for 16 h and poured over ether (200 mL) and ice water (150 mL), and stirring was continued for 5 min, after which time 10% HCl in water (50 mL) was added. The organic phase was separated and the aqueous phase extracted with ether (2 × 20 mL). The combined organic phases were washed with saturated brine (20 mL) and water (20 mL), dried, and concentrated, yielding the tosylate **26**, which was reduced without purification.

To a suspension of $LiAlH_4$ (180 mg, 4.75 mmol) in THF (95 mL) was added slowly the crude tosylate **26** at 0 °C. The reaction mixture was allowed to reach room temperature and stirred for 4 h. Water (10 mL) and 10% HCl aqueous solution (20 mL) were added sequentially to quench the reaction, and stirring was continued until clear phases were reached. The organic phase was separated and the aqueous phase extracted with ether (2 × 10 mL). The combined organic phases were washed with saturated aqueous $NaHCO_3$ (20 mL) and water (20 mL), dried, and concentrated. Purification by column chromatography gave **27** (1.13 g, 72% yield): mp 37–38 °C (lit.[29] mp 38 °C); $[\alpha]^{25}_D$ −25.0° (*c* 1.02, EtOH) [a value of $[\alpha]^{25}_D$ +23° (*c* 1.04, EtOH) has been reported for (3*S*)-1-phenyl-3-pentanol of ≈80% optical purity];[29a] ^1H NMR δ 0.95 (t, J = 7.4, 3 H), 1.50 (m, 2 H), 1.77 (m, 2 H), 2.74 (m, 2 H), 3.57 (m, 1 H), 7.23 (m, 5 H); ^{13}C NMR δ 10.01 (q), 30.47 (t), 32.26 (t), 38.76 (t), 72.84 (d), 125.97 (d), 128.58 (d); IR ($CHCl_3$) (cm^{-1}) 3400, 3000, 930; MS m/z (relative intensity) 164 (2), 163 (3), 146 (9), 144 (17), 129 (26), 91 (100); HRMS calcd for $C_{11}H_{16}O$ 164.1201, obsd 164.1213.

(3*R*)-1-Phenyl-3-(acetyloxy)pentane (28). To a cooled solution (0 °C) of **27** (1.11 g, 6.80 mmol) in dry pyridine (10 mL)

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was added acetic anhydride (1 mL, 10.6 mmol) with stirring. The reaction mixture was allowed to reach room temperature and stirred for 2 h. Water (10 mL), ether (50 mL), and 10% HCl in water (30 mL) were added sequentially with vigorous stirring. The organic phase was separated and the aqueous phase extracted with ether (2 × 10 mL). The combined organic phases were washed with saturated brine, a saturated solution of $NaHCO_3$, and brine, dried, and concentrated. Purification by column chromatography gave **28** (1.33 g, 96% yield): $[\alpha]^{25}_D$ +12.1° (*c* 11.5, EtOH) (lit.[30] for the 3*S* isomer $[\alpha]^{18.5}_{546}$ −11.5°); ^{1}H NMR δ 0.81 (t, *J* = 7.3 Hz, 3 H), 1.46 (m, 2 H), 1.75 (m, 2 H), 1.96 (s, 3 H), 2.56 (m, 2 H), 4.80 (m, 1 H), 7.15 (m, 5 H); ^{13}C NMR δ 15.79 (q), 27.45 (q), 33.32 (t), 38.10 (t), 41.60 (t), 81.35 (d), 132.17 (d), 134.60 (d), 134.69 (d); IR ($CHCl_3$) (cm^{-1}) 3010, 2990, 2910, 1710, 1280; MS *m/z* (relative intensity) 206 (1), 146 (42), 117 (100), 104 (53), 91 (69); HRMS calcd for $C_{13}H_{18}O_2$ 206.1307, obsd 206.1292.

(4*R*)-4-(Acetyloxy)hexanoic Acid (29). The oxidation reaction of **28** was performed on a 6.45-mmol (1.33 g) scale in accordance with the general procedure (large scale). After 2.5 h, the reaction was complete and the workup was carried out as described above (general procedure), providing **29** (0.81 g, 72% yield): $[\alpha]^{25}_D$ +0.93° (*c* 10.2, EtOH); ^{1}H NMR δ 0.86 (t, *J* = 7.2 Hz, 3 H), 1.55 (m, 2 H), 1.81 (m, 2 H), 2.02 (s, 3 H), 2.35 (t, *J* = 7.4 Hz, 2 H), 4.81 (m, 1 H), 9.1 (s, 1 H); ^{13}C NMR δ 9.55 (q), 21.12 (q), 26.99 (t), 28.47 (t), 30.15 (t), 74.58 (d), 171.25 (s), 179.14 (s); IR (film) (cm^{-1}) 3450, 3000, 2930, 1720, 1360, 1020, 940; MS *m/z* (relative intensity) 174 (1), 157 (1), 115 (16), 91 (2), 85 (100); HRMS calcd for $C_8H_{14}O_4$ 174.0892, obsd 174.0913.

(4*R*)-γ-Caprolactone (30). To a solution of the acid **29** (800 mg, 4.6 mmol) in ether (10 mL) was added a 30% NaOH aqueous solution saturated in brine (10 mL), and the mixture was vigorously stirred for 1 h at room temperature. The aqueous layer was separated, treated with concentrated HCl (10 mL), and stirred for 0.5 h. The reaction mixture was extracted with ether (3 × 10 mL). The combined organic phases were washed with saturated $NaHCO_3$ (10 mL) and brine, dried, and carefully concentrated to an oil, which was purified by bulb-to-bulb distillation, without vacuum, to obtain **30** (0.38 g, 73% yield): bp 215–225 °C; $[\alpha]^{25}_D$ +50.8° (*c* 1.3, MeOH) [lit.[23] $[\alpha]^{20}_D$ +53.2° (*c* 1.0, MeOH)]; ^{1}H NMR δ 1.01 (t, *J* = 7.0 Hz, 3 H), 2.09 (m, 6 H), 4.43 (m, 1 H); ^{13}C NMR δ 9.56 (q), 27.65 (t), 28.66 (t), 29.03 (t), 66.01 (nd), 177.55 (s); IR ($CHCl_3$) (cm^{-1}) 2990, 1740, 1420, 1150; MS *m/z* (relative intensity) 114 (2), 86 (17), 85 (100), 60 (92); HRMS calcd for $C_6H_{10}O_2$ 114.0681, obsd 114.0657.

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Diastereoselective Additions of (*R*)-(+)-Methyl *p*-Tolyl Sulfoxide Anion to Imines. Asymmetric Synthesis of (*R*)-(+)-Tetrahydropalmatine[1]

Stephen G. Pyne* and Branko Dikic

Department of Chemistry, University of Wollongong, P.O. Box 1144, N.S.W. 2500, Australia

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The addition of the lithium carbanion of methyl phenyl sulfoxide and (*R*)-(+)-methyl *p*-tolyl sulfoxide to imines having at least one aryl substituent, under kinetically controlled conditions, gives β-amino sulfoxides with good to modest diastereoselection. Under equilibrium controlled condition poor product diastereoselection results. The addition of these anions to 3,4-dihydro-6,7-dimethoxyisoquinoline is unique in that the most favorable product diastereoselection (92:8) is observed under equilibrium controlled conditions. Deuteration experiments suggest that equilibration occurs via a β-amino α-lithio sulfinyl carbanion through a retro-Michael addition then Michael addition reaction sequence. This methodology allows for the construction of (*R*)-(+)-tetrahydropalmatine in four efficient synthetic steps.

A prominent structural feature of a large number of alkaloids and pharmacologically active amines is a chiral carbon that has a nitrogen substituent. Several asymmetric synthetic method have been recently reported for the preparation of these types of compounds.[2] We have demonstrated that enantiomerically pure β-amino sulfoxides are versatile intermediates for chiral alkaloid synthesis.[3] Chiral β-amino sulfoxides can be conveniently prepared by either conjugate addition of amines to chiral vinyl sulfoxides[3,4] or from the addition of a chiral α-sulfinyl

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