

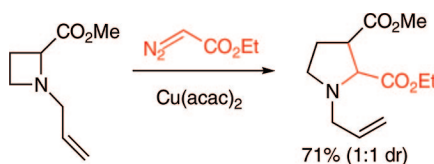
One-Carbon Ring Expansion of Azetidines via Ammonium Ylide [1,2]-Shifts: A Simple Route to Substituted Pyrrolidines

Tina M. Bott,[†] John A. Vanecko,^{§,‡} and F. G. West^{*,†}

Department of Chemistry, University of Alberta, E3-43 Gunning-Lemieux Chemistry Centre, Edmonton, AB T6G 2G2, Canada, and Department of Chemistry, University of Utah, 315 S. 1400 East, Rm 2020, Salt Lake City, Utah 84112

frederick.west@ualberta.ca

Received January 22, 2009



Simple *N*-substituted azetidines were heated with diazocarbonyl compounds in the presence of catalytic $\text{Cu}(\text{acac})_2$ to furnish substituted pyrrolidines via Stevens [1,2]-shift. In all but two examples, complete selectivity was seen for ring expansion rather than migration of the other exocyclic group on the azetidinium nitrogen. The two exceptions, observed with ylides substituted with two carbonyl groups and lacking a stabilizing group at the 2-position of the azetidine, underwent exocyclic benzyl migration in preference to ring expansion.

Introduction

The pyrrolidine skeleton is found in a variety of settings. For example, many naturally occurring alkaloids possess one or more pyrrolidine rings.¹ A large number of unnatural, biologically active substances also contain the pyrrolidine substructure.² Finally, pyrrolidines are prominently featured in a number of organocatalytic processes.³ Given their importance, it is not surprising that many elegant methods have been developed for the synthesis of pyrrolidines.⁴

One-carbon ring expansion of ammonium ylides via the Stevens rearrangement⁵ has proven to be a convenient and versatile entry to various nitrogen-containing heterocycles,

especially those containing one or more piperidine rings.⁶ More recently, this methodology has been applied to the synthesis of the pyrrolizidine alkaloids turneforcidine and platynecine.⁷ As part of that work, a preliminary model study was carried out in which intermolecular addition of a catalytically generated metallocarbene to a simple azetidine furnished a protected 3-carboxypyrrolidine **4a** as an inseparable mixture of diastereomers in good yield via an intermediate azetidinium ylide **3a** (eq 1). Regioselective migration of the ester-substituted carbon of **3a** (with concomitant ring expansion)⁸ in preference to benzyl migration was noteworthy, as it suggested that azetidine ring strain could overcome the inherent ammonium ylide migratory preferences seen in simple acyclic examples.⁹ Moreover, efficient intermolecular trapping of the metallocarbene by a simple azetidine, if general, could offer a novel and convenient method for the construction of substituted pyrrolidines from two readily available building blocks. Here we describe the results from a

[†] University of Alberta.

[§] Current address: Amgen Inc., One Amgen Center Drive, Thousand Oaks, CA, 91320-1799, USA.

[‡] University of Utah.

(1) (a) Michael, J. P. *Nat. Prod. Rep.* **2008**, 25, 139–165. (b) Vanecko, J. A.; West, F. G. *Heterocycles* **2007**, 74, 125–143. (c) Daly, J. W.; Spande, T. F.; Garraffo, H. M. *J. Nat. Prod.* **2005**, 68, 1556–1575. (d) Pyne, S. G.; Davis, A. S.; Gates, N. J.; Hartley, J. P.; Lindsay, K. B.; Machan, T.; Tang, M. *Synlett* **2004**, 2670–2680. (e) Felpin, F.-X.; Lebreton, J. *Eur. J. Org. Chem.* **2003**, 369, 3–3712.

(2) (a) Bellina, F.; Rossi, R. *Tetrahedron* **2006**, 62, 7213–7256. (b) Cheng, X.-C.; Wang, Q.; Fang, H.; Xu, W.-F. *Curr. Med. Chem.* **2008**, 15, 374–385.

(3) (a) Gruttadauria, M.; Giacalone, F.; Noto, R. *Chem. Soc. Rev.* **2008**, 37, 1666–1688. (b) Ting, A.; Schaus, S. E. *Eur. J. Org. Chem.* **2007**, 5797–5815. (c) Guillena, G.; Najera, C.; Ramon, D. J. *Tetrahedron: Asymmetry* **2007**, 18, 2249–2293.

(4) (a) Minatti, A.; Muniz, K. *Chem. Soc. Rev.* **2007**, 36, 1142–1152. (b) Wolfe, J. P. *Eur. J. Org. Chem.* **2007**, 57, 1–582.

(5) Vanecko, J. A.; Wan, H.; West, F. G. *Tetrahedron* **2006**, 62, 1043–1062.

(6) (a) Glaeske, K. W.; Naidu, B. N.; West, F. G. *Tetrahedron: Asymmetry* **2003**, 14, 917–920. (b) Naidu, B. N.; West, F. G. *Tetrahedron* **1997**, 53, 16565–16574. (c) West, F. G.; Naidu, B. N. *J. Am. Chem. Soc.* **1993**, 115, 1177–1178.

(7) Vanecko, J. A.; West, F. G. *Org. Lett.* **2005**, 7, 2949–2952.

(8) For other examples of azetidinium ylide ring expansions, see: (a) Couty, F.; Durrat, F.; Evano, G.; Marrot, J. *Eur. J. Org. Chem.* **2006**, 4214–4223. (b) Wills, M. T.; Wills, I. E.; Von Dollen, L.; Butler, B. L.; Porter, J.; Anderson, A. G. *J. Org. Chem.* **1980**, 45, 2489–2498. (c) Hatu, Y.; Watanabe, M. *Tetrahedron Lett.* **1972**, 46, 4659–4660.

(9) West, F. G.; Glaeske, K. W.; Naidu, B. N. *Synthesis* **1993**, 977–980.

(10) For other applications of azetidinium ylides, see: (a) Alex, A.; Larmanjat, B.; Marrot, J.; Couty, F.; David, O. *Chem. Commun.* **2007**, 2500–2502. (b) Couty, F.; David, O.; Larmanjat, B.; Marrot, J. *J. Org. Chem.* **2007**, 72, 1058–1061.

TABLE 2. Effect of Structural Variation of **1** and **2**^a

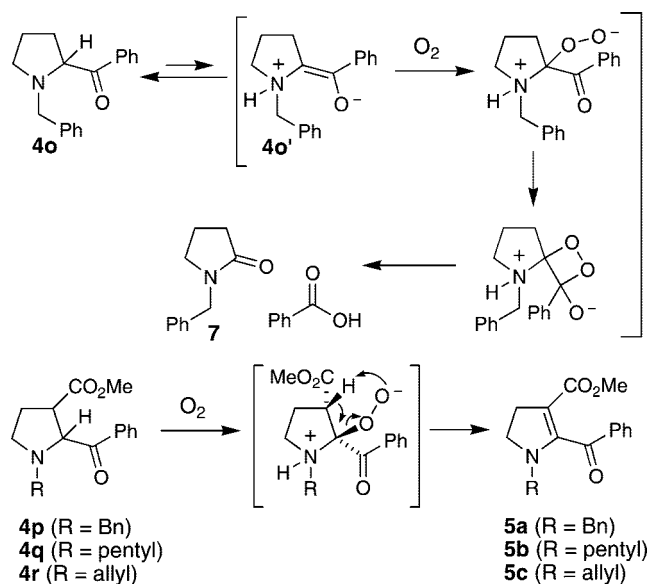
	azetidine	R ¹	R ²	R ³	diazocarbonyl	R ⁴	R ⁵	method	product	yield (%) ^b
1	1a	Bn	CO ₂ Me	H	2b	OEt	CO ₂ Et	B	4b	81
2	1a	Bn	CO ₂ Me	H	2a	OEt	H	B	4a	66
3	1a	Bn	CO ₂ Me	H	2d	OEt	COPh	A	— ^c	— ^c
4	1b	C ₅ H ₁₁	CO ₂ Me	H	2a	OEt	H	B	4d	62
5	1b	C ₅ H ₁₁	CO ₂ Me	H	2b	OEt	CO ₂ Et	B	4e	60
6	1b	C ₅ H ₁₁	CO ₂ Me	H	2d	OEt	COPh	A	4f	20
7	1c	allyl	CO ₂ Me	H	2a	OEt	H	B	4g	71
8	1c	allyl	CO ₂ Me	H	2b	OEt	CO ₂ Et	B	4h	69
9	1c	allyl	CO ₂ Me	H	2d	OEt	COPh	A	4i	32
10	1a	Bn	CO ₂ Me	H	2c	Ph	H	B	5a	34
11	1b	C ₅ H ₁₁	CO ₂ Me	H	2c	Ph	H	B	5b	65
12	1c	allyl	CO ₂ Me	H	2c	Ph	H	B	5c	48
13	1d	Bn	Me	Me	2a	OEt	H	B	4j	62
14	1d	Bn	Me	Me	2b	OEt	CO ₂ Et	B	— ^c	— ^c
15	1d	Bn	Me	Me	2c	Ph	H	B	4l	24
16	1d	Bn	Me	Me	2d	OEt	COPh	B	— ^c	— ^c
17	1e	Bn	H	H	2a	OEt	H	A ^d	4n	67 ^e
18	1e	Bn	H	H	2b	OEt	CO ₂ Et	A	6a	59
19	1e	Bn	H	H	2c	Ph	H	A	4o	39 ^f
20	1e	Bn	H	H	2d	OEt	COPh	A	6b	21

^a Method A: See Table 1, footnote a. Method B: A solution of **2** (1.5 equiv) in ClCH₂CH₂Cl (0.5 M) was added to a solution of **1** and Cu(acac)₂ (10 mol %) in ClCH₂CH₂Cl (0.05M) in a 5 mL Biotage microwave vial. The vial was sealed and the resulting mixture was subjected to microwave irradiation (150–180 °C) in a Biotage Initiator microwave reactor for 1 h. After cooling, the reaction mixture was washed with an equivalent volume of 0.5 M aqueous K₂CO₃ and brine, dried over MgSO₄, filtered, concentrated, and purified by flash chromatography. ^b All yields given are for isolated product after chromatographic purification. Under the conditions of method B, 9–20% of alkene product from dimerization of diazo compounds **2** was also isolated. ^c Diazo compound **2d** was consumed very slowly, in most cases furnishing a complex mixture containing diazo dimers and unreacted **1** (entries 3, 14, and 16). ^d For this reaction, Cu powder (50 mol %) was used in place of Cu(acac)₂ and an additional filtration through celite to remove residual Cu powder was added to the workup procedure. ^e Following an unspecified procedure, Hatu and Watanabe reported a yield of 96% in this transformation, using Cu(acac)₂ (see ref 8c). ^f A crude yield of 39% could be obtained in the case of pyrrolidine **4o**, but purification was complicated by its rapid conversion to lactam **7**.

process could still be viable in the absence of a stabilizing substituent on the migrating carbon.^{8c} In the event, both **1d** and **1e** underwent reaction with **2a** and **2c** to give pyrrolidines **4j**, **4n**, **4o** in modest to good yields (entries 13, 15, 17, and 19). However, none of the desired pyrrolidine product was obtained with **2b**, **2d**. In the case of **1d**, only uncharacterizable polar materials were formed, while with **1e** the benzyl [1,2]-shift products **6a**, **6b** were formed (entries 18 and 20).

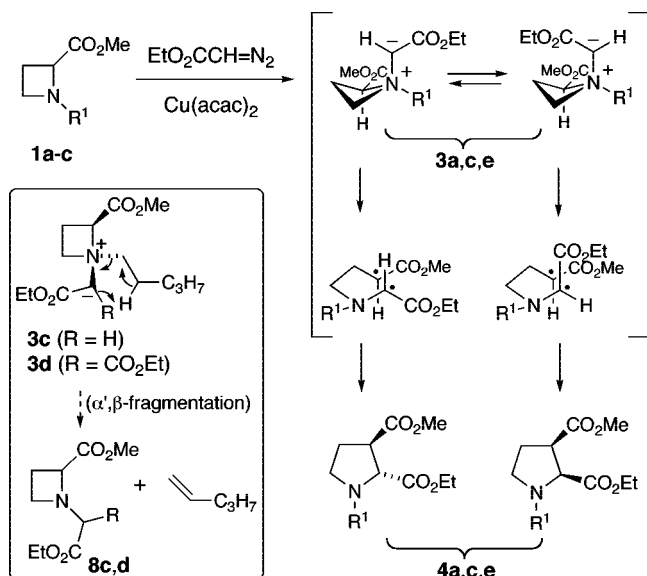
Adducts derived from diazoacetophenone **2c** showed unusual lability. As noted above, with ester-substituted azetidines **1a–c**, only pyrrolines **5** were isolated, in moderate yields. In the case of the simple *N*-benzylazetidine **1e**, the expected pyrrolidine **4o** was isolated, but it underwent rapid and apparently quantitative conversion to *N*-benzylpyrrolidinone **7** during handling and attempted chromatographic purification. This process, an apparent debenzoylative oxidation, may involve reaction of the ylide tautomer of **4o** (**4o'**) with ambient oxygen (Scheme 1).¹⁵ It is also possible that the dehydrogenation products **5a–c** may result from an alternative elimination pathway following reaction

SCHEME 1. Oxidative Decomposition of Benzoyl-Substituted Products



(15) (a) Facile aerobic debenzoylative oxidation of α -aminoketones under basic conditions has been observed by García-Valverde and co-workers: García-Valverde, M.; Pedrosa, R.; Vicente, M. *Synlett* **2002**, 2092–2093. (b) For a related oxidative deacylation, see: Yijima, C.; Hino, F.; Suda, K. *Synthesis* **1981**, 610–611.

of intermediate pyrrolidines **4p–r** with oxygen. Intervention of these unexpected processes in benzoyl-substituted examples

SCHEME 2. Radical Pair Mechanism for the Stevens [1,2]-Shift


may be due to the greater acidity of the adjacent α proton in comparison to carboethoxy-substituted cases (e.g., **4a,d,g,j,n**), and no such reactivity is expected from malonate- or ketoester-derived products, due to the absence of an acidic proton adjacent to the ring nitrogen.

The Stevens [1,2]-shift of ammonium ylides is believed to involve a stepwise homolytic mechanism (Scheme 2).¹⁶ In light of the likely intermediacy of a biradical, it is not surprising that pyrrolidines **4a,d,f,g,i** were formed as diastereomeric mixtures. In the case of spirocyclic ammonium ylides resulting from intramolecular metallocarbene addition high diastereoselectivity was seen, with high levels of retention of configuration during migration of an ester-substituted center.⁶ On the other hand, with monocyclic ylides such as **3**, although face-selective metallocarbene addition *cis* to the neighboring ester is expected to predominate,¹⁷ both rotamers of the exocyclic ylide N–C bond are likely to be present. Even if the subsequent [1,2]-shift occurred with retention, both diastereomers would be expected. Moreover, if the biradical intermediate persists long enough to randomize, little diastereoselectivity would be expected in the eventual radical recombination step.¹⁸

The radical center, residing at the former ylide carbon, is stabilized by both the electron-withdrawing substituent and the basic nitrogen.¹⁹ Typically, the migrating group is substituted with a moiety able to stabilize the other radical center through conjugation (e.g., aryl, alkenyl, or carbonyl). If there is more

than one competent migrating group on the ammonium nitrogen, selective rearrangement is possible if there is a significant energetic difference between the two possible radical pairs. In the specific case of azetidine **1a**, exclusive formation of pyrrolidines **4a,b** indicates that release of ring strain is a significant factor in bond homolysis selectivity, since benzyl groups show greater migratory aptitude than $\text{CH}_2\text{CO}_2\text{R}$ in acyclic substrates. The *n*-pentyl group of **1b** is expected to have limited migratory aptitude, so successful ring expansion in those cases is not surprising. The presence of β -hydrogens on the side chain does permit a possible α',β -fragmentation process by the intermediate ylide; however, no evidence was seen for the formation of the simple dealkylation products **8c,d**. As with **1a**, rapid homolytic ring opening appears to be the predominant fate of the azetidinium ylide.

Observation of exclusive ring expansion by *N*-allyl substrate **1c** merits further comment. While the allyl group is capable of undergoing Stevens [1,2]-shift via the usual radical pair mechanism, the alternative concerted [2,3]-shift process is also possible. In those cases where both rearrangement pathways are possible, the [2,3]-shift appears to occur more readily for ammonium,²⁰ sulfonium,²¹ and oxonium²² ylides, presumably due to a lower activation barrier for the concerted process. The absence of *any* [2,3]-shift product from **1c** again indicates the important effect of ring strain in azetidinium ylide rearrangements.

Azetidines **1d,e** lacking a conjugating group on the migrating carbon were chosen to test the limits of ring strain as a predisposing factor in migratory aptitude. *gem*-Dimethyl substitution in the case of **1d** was expected to provide moderate stabilization of the radical intermediate, consistent with other examples of [1,2]-shift by tertiary radicals lacking any conjugating groups.²³ In fact, a surprisingly good yield of *N*-benzyl-3,3-dimethylproline ethyl ester **4j** was obtained, with no evidence for competing benzyl shift. Formation of the corresponding benzoyl-substituted **4l** in only modest yield is disappointing, but oxidative decomposition analogous to that seen for **4o** may be occurring.²⁴ The failure to observe comparable results with diazo partners **2b,d** is puzzling, and requires further investigation. The behavior of the simple *N*-benzylazetidine **1e** is especially intriguing. As mentioned above, Hatu and Watanabe had previously reported successful ring expansion to provide protected proline **4n**, a result that we confirmed. Likewise, treatment with diazoacetophenone also leads to pyrrolidine product (**4o**). However, doubly stabilized ylides derived from diazomalonate or the corresponding ketoester provide only the benzyl [1,2]-shift products **6a,b**. Failure to react via the ring expansion pathway in these cases indicates the limits of ring strain as a deciding factor in migratory selectivity. It is possible that doubly stabilized ammonium ylides, which are generally slower to rearrange than their monostabilized counterparts, are more sensitive to the stability of the radical on the

(16) (a) Heard, G. L.; Yates, B. F. *Aust. J. Chem.* **1995**, *48*, 1413–1423. (b) Ollis, W. D.; Rey, M.; Sutherland, I. O. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1009–1027.

(17) (a) Vedejs, E.; Arco, M. J.; Powell, D. W.; Renga, J. M.; Singer, S. P. *J. Org. Chem.* **1978**, *43*, 4831–4837. (b) Kawanishi, N.; Fujiwara, K.; Shirai, N.; Sato, Y.; Hatano, K.; Kurono, Y. *J. Chem. Soc., Perkin Trans. 1* **1997**, 3013–3016. (c) Glaeske, K. W.; West, F. G. *Org. Lett.* **1999**, *1*, 31–33.

(18) Epimerization of one or both stereocenters may also occur during the reaction. However, since the diastereomeric mixtures were inseparable, it was not possible to probe for this by resubjecting pure diastereomers to the reaction conditions.

(19) (a) Welle, F. M.; Beckhaus, H.-D.; Rüchardt, C. *J. Org. Chem.* **1997**, *62*, 552–558. (b) Schulze, R.; Beckhaus, H.-D.; Rüchardt, C. *Chem. Ber.* **1993**, *126*, 1031–1038.

(20) (a) Roberts, E.; Sançon, J. P.; Sweeney, J. B. *Org. Lett.* **2005**, *7*, 2075–2078. (b) Jemison, R. W.; Laird, T.; Ollis, W. D.; Sutherland, I. O. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1450–1461.

(21) Vedejs, E.; Arnost, M. J.; Hagen, J. P. *J. Org. Chem.* **1979**, *44*, 3230–3238.

(22) (a) West, F. G.; Eberlein, T. H.; Tester, R. W. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2857–2859. (b) Marmasäter, F. P.; Vanecko, J. A.; West, F. G. *Tetrahedron* **2002**, *58*, 2027–2040. (c) For the role of transition metal catalysts in periselectivity, see: Marmasäter, F. P.; Vanecko, J. A.; West, F. G. *Org. Lett.* **2004**, *6*, 1657–1660.

(23) (a) Tester, R. W.; West, F. G. *Tetrahedron Lett.* **1998**, *39*, 4631–4634. (b) West, F. G.; Naidu, B. N. *J. Org. Chem.* **1994**, *59*, 6051–6056.

(24) None of the 3,3-dimethyl-2-pyrrolidinone product analogous to **7** was isolated from reaction of **1d** with **2c**.

(25) For a related example of exclusive benzyl migration rather than ring expansion of an azetidinium ylide stabilized by ester and trifluoromethyl groups, see: Osipov, S. N.; Sewald, N.; Kolomiets, A. F.; Fokin, A. V.; Burger, K. *Tetrahedron Lett.* **1996**, *37*, 615–618.

migrating center.²⁵ Further competition experiments with other nonconjugating substituents on the migrating carbon may help clarify this issue.

Conclusion

A general method for the preparation of substituted pyrrolidines has been described. Heating two readily available reactants, an *N*-substituted azetidine and a diazocarbonyl compound, in the presence of catalytic Cu(acac)₂ results in the formation of an azetidinium ylide via addition of a transient metallocarbene to the basic nitrogen of the azetidine. Microwave heating usually gives cleaner reactions and higher yields over much shorter reaction times. In most cases the ylide undergoes regioselective [1,2]-shift of an azetidine ring carbon, leading to ring expanded products, even when competent migrating groups such as benzyl or allyl are present as exocyclic nitrogen substituents. A range of substitution patterns is tolerated on the migrating center, including (in the case of monostabilized metallocarbenes) CH₂. For examples leading to two adjacent stereocenters no diastereoselectivity is observed. Future efforts will focus on control of relative and absolute configuration, as well as the delineation of factors controlling migratory aptitude in ylides lacking a strongly stabilizing group at the azetidine C-2 position.

Experimental Section

General Procedures for Ring Expansions. Method A: a solution of azetidine **1** and catalyst in PhCH₃ (0.025 M) was heated to reflux, and a solution of diazo compound **2** (0.67 equiv) in PhCH₃ (0.1 M) was added via syringe pump over a 12 h period. Following completion of addition, the reaction mixture was cooled to rt then washed with an equivalent volume of 0.5 M aqueous K₂CO₃ solution and brine, dried over MgSO₄, filtered, concentrated under reduced pressure, and purified by flash chromatography. **Method B:** A solution of **2** (1.5 equiv) in ClCH₂CH₂Cl (0.5 M) was added to a solution of **1** and Cu(acac)₂ (10 mol %) in ClCH₂CH₂Cl (0.05 M) in a 5 mL Biotage microwave vial. The vial was sealed and the resulting mixture was subjected to microwave irradiation (150–180 °C) in a Biotage Initiator microwave reactor for 1 h. (See the

Supporting Information for a description of temperature monitoring in microwave reactions.) After cooling, the reaction mixture was washed with an equivalent volume of 0.5 M aqueous K₂CO₃ and brine, dried over MgSO₄, filtered, concentrated, and purified by flash chromatography.

1-Benzylpyrrolidine-2,3-dicarboxylic acid 3-methyl 2-ethyl ester 4a (1:1 mixture of diastereomers as determined by integration of the OMe singlets in the ¹H NMR spectrum): *R*_f 0.17 (2:3 EtOAc/hexanes); IR (thin film) 2979, 2954, 2839, 1740, 1603, 1495, 1453 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.34–7.22 (m, 10H), 4.21–4.09 (m, 4H), 3.99 (d, *J* = 12.9 Hz, 1H), 3.83–3.70 (m, 3H), 3.71 (s, 3H), 3.65 (s, 3H), 3.58 (d, *J* = 2.9 Hz, 1H), 3.54 (d, *J* = 3.6 Hz, 1H), 3.33–3.21 (m, 2H), 3.06–2.98 (m, 2H), 2.71 (ddd, *J* = 8.8, 7.4, 7.4 Hz, 1H), 2.56–2.47 (m, 1H), 2.35 (dddd, *J* = 12.7, 9.2, 9.2, 7.4 Hz, 1H), 2.22–2.02 (m, 3H), 1.26 (t, *J* = 7.2 Hz, 3H), 1.25 (t, *J* = 7.2 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 174.5, 172.8, 172.7, 171.5, 138.4, 138.4, 129.2, 129.1, 128.4, 127.4, 127.3, 68.4, 66.2, 61.2, 60.7, 58.8, 57.2, 52.8, 52.4, 52.1, 51.5, 47.3, 46.6, 27.7, 26.7, 14.5, 14.4.

1-Benzylpyrrolidine-2,2,3-tricarboxylic acid 3-methyl 2,2-diethyl ester 4b: IR (thin film) 2982, 2842, 1731, 1495, 1454, 1367, 1214, 1098, 1028 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.37–7.35 (m, 2H), 7.29–7.26 (m, 2H), 7.22–7.19 (m, 1H), 4.34–4.20 (m, 4H), 3.97 (d, *J* = 13.5 Hz, 1H), 3.85 (d, *J* = 13.5 Hz, 1H), 3.71 (dd, *J* = 9.0, 8.4 Hz, 1H), 3.68 (s, 3H), 2.92 (app td, *J* = 8.8, 4.7 Hz, 1H), 2.81 (app td, 8.5, 6.8 Hz, 1H), 2.24–2.13 (m, 2H), 1.30 (app t, *J* = 7.1 Hz, 3H), 1.29 (app t, *J* = 7.2 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 172.3, 169.1, 168.7, 139.6, 128.3, 128.2, 126.9, 76.9, 61.6, 61.3, 54.8, 52.0, 51.1, 50.4, 26.1, 14.2, 14.1; HRMS calcd for C₁₉H₂₅NO₆Na (M + Na) 386.1574, found 386.1577.

Acknowledgment. This work was supported by NSERC (Canada) and the donors of the Petroleum Research Fund, administered by the American Chemical Society. T.B. thanks NSERC for a PGSM award and the University of Alberta for a Queen Elizabeth II scholarship.

Supporting Information Available: NMR spectra for **4b,d–j**, **5a–c**, and **6a,b**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

JO9001323