JOURNAL OF combinatorial CHEMISTRY

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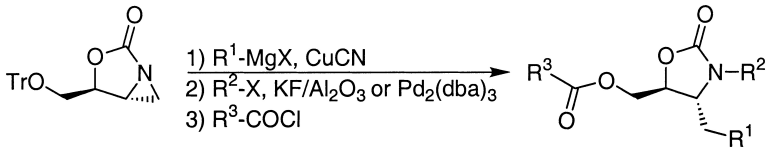
J. Comb. Chem., **2002**, 4 (2), 162-166• DOI: 10.1021/cc010050f • Publication Date (Web): 18 January 2002



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A Method for the Parallel Synthesis of Multiply Substituted Oxazolidinones

Stephen C. Bergmeier* and Steven J. Katz

Department of Chemistry and Biochemistry, Ohio University, Athens, Ohio 45701

Received July 31, 2001

There are many examples of both naturally occurring and synthetic molecules containing a 2-oxazolidinone ring that have significant biological activity. The oxazolidinone ring potentially has three sites for attachment of diversity elements. A synthesis that can provide for inclusion of diversity elements at all three positions should be a powerful method for the preparation of oxazolidinone libraries. In this paper we present the preparation of a 3 × 3 × 3 array yielding 27 different products with minimal workup, high yields, and, most importantly, high purity. Using an intramolecular acylnitrene-mediated aziridination reaction, we have prepared (triphenylmethoxymethyl)-3-oxa-1-azabicyclo[3.1.0]hexan-2-one as a starting material for library generation. The first substitution involves opening the aziridine ring of the azabicyclo[3.1.0]hexane ring system using a Grignard reagent. The nitrogen of the oxazolidinone is now ready for substitution via alkylation or arylation. Removing the trityl protecting group via esterification under mildly acidic conditions accomplishes the final substitution.

Introduction

The 2-oxazolidinone ring is formed in many naturally occurring and synthetic molecules often with significant biological activity. An example is cytoxazone (Figure 1), an alkaloid isolated from a *Streptomyces* sp. This oxazolidinone is an immunomodulator that inhibits intercellular communication between Th1 and Th2 macrophages.[1] The oxazolidinone ring is also a component of a novel class of synthetic antimicrobial agents (e.g., DuP 721; Figure 1) with activity against multidrug-resistant Gram-positive bacteria.[2] An oxazolidinone analogue of the muscarinic agonist pilocarpine is equipotent to pilocarpine and used for the treatment of glaucoma. This means that the oxazolidinone analogue has the flexibility to adopt the necessary receptor-active configuration.[3] Another series of oxazolidinones receiving a lot of interest are the spirooxazolidinones. AR-R17779 (Figure 1) has been found to be a strong agonist at the rat α7 nicotinic receptor.[4] Such agonists have been used in the treatment of neurodegenerative diseases (e.g., Alzheimer's disease).

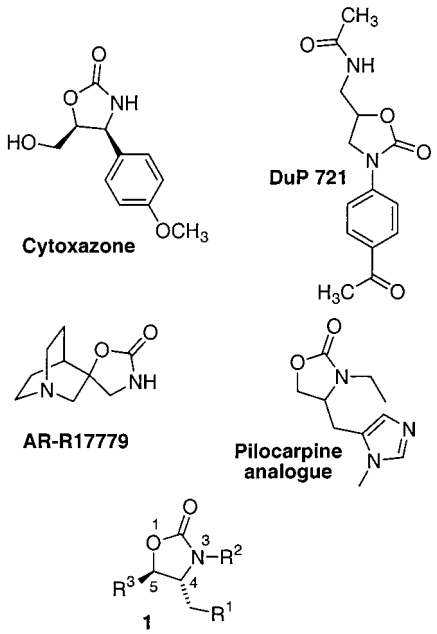


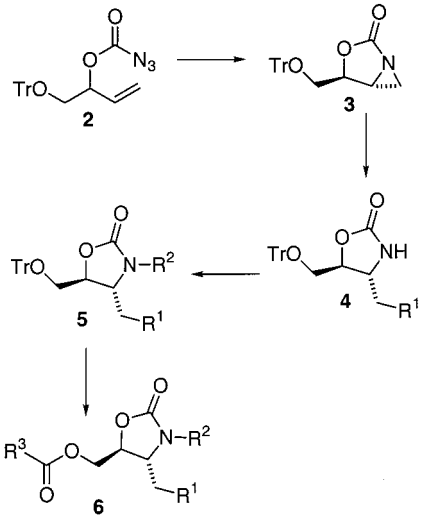
Figure 1.

The oxazolidinone ring potentially has three sites for attachment of diversity elements, N-3, C-4, and C-5. Additionally one has the relative stereochemistry at C-4 and C-5 that can be controlled. A synthesis that can provide for inclusion of diversity elements at N-3, C-4, and C-5 as well as control the C-4/C-5 relative stereochemistry should be a powerful method for the preparation of oxazolidinone libraries. Given the range of biological activity seen with 2-oxazolidinones, such a method should have wide applicability.

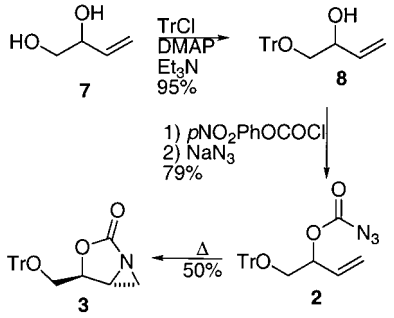
There are a variety of methods for the synthesis of oxazolidinones.[5−13] Our synthetic plan (Scheme 1) uses a method previously developed in our laboratory that is well suited to the preparation of compound libraries.[14,15] This method utilizes an intermolecular acylnitrene-mediated aziridination to form the bicyclic aziridine **3**. The aziridine ring is opened with a nucleophile to provide oxazolidinone **4**. Our method of oxazolidinone formation has the advantage of ready introduction of diversity at the 4 position of the oxazolidinone ring. Oxazolidinone **4** is substituted on the nitrogen via a variety of methods to produce **5**. Finally the trityl ether can be readily converted to **6** in a single pot by reaction with an acid chloride.[16] To demonstrate the utility of this strategy, we have prepared a 3 × 3 × 3 array of substituted oxazolidinones.

10.1021/cc010050f CCC: $22.00
Published on Web 01/18/2002

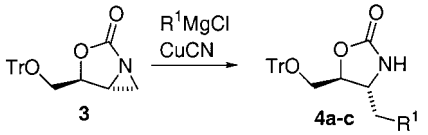
Scheme 1



Scheme 2



Scheme 3



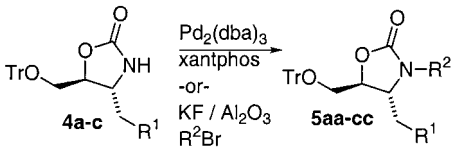
4a, R^1 = Ph
4b, R^1 = $PhCH_2CH_2$
4c, R^1 = cyclohexyl

Results and Discussion

The bicylic aziridine **3** was prepared as shown in Scheme 2. The primary hydroxyl group of diol **7**[17] was protected as the trityl ether **8** in excellent yield. When our previously reported method was used, alcohol **8** was converted to azidoformate **2**.[15] Thermolysis of the azidoformate **2** provided bicyclic aziridine **3** in good yield as a single diastereomer. The bicyclic aziridine **3** is a useful starting point for the elaboration of substituted oxazolidinones. Unlike previously prepared bicyclic aziridines, aziridine **3** is a stable, isolable solid that can be purified by recrystallization. Other bicyclic aziridines that we have prepared are somewhat unstable both to storage and to purification.[14,15]

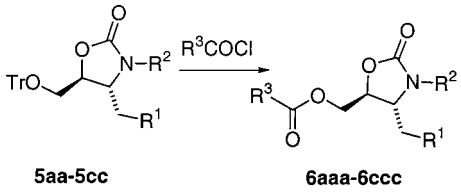
Our synthesis of a demonstration library starts with the opening of the aziridine ring of **3** with a copper-catalyzed Grignard reagent as shown in Scheme 3. The availability of Grignard reagents is quite good, and a wide variety of them are available commercially as well. All of the Grignard reagents that we have used are commercially available. We have previously shown that this is a general reaction that

Scheme 4



5_a, R^2 Br= methyl 2-bromobenzoate
5_b, R^2 Br= 4-bromoanisole
5_c, R^2 Br= 1-bromobutane

Scheme 5



6_ _a, R^3 = $PhCH_2$
6_ _b, R^3 = cyclohexyl
6_ _c, R^3 = nC_7H_{15}

tolerates a wide variety of organometallic reagents.[14,15] This reaction proceeds in generally high yields and provides compounds of excellent purity. After an aqueous workup, GC/MS and ^{1}H NMR showed that all of these compounds were >77% pure. Compounds **4a**−**c** were portioned into thirds and carried on to the next step without any further purification.

We next planned to substitute the nitrogen with both aryl and alkyl groups (R^2). Substitution with an aliphatic group is the most straightforward with a variety of methods available to carry out this transformation. We have chosen to use the KF/Al_2O_3 method because the base can be readily filtered off when the reaction is complete.[18] Each of the compounds **4a**−**c** were treated with KF/Al_2O_3 and bromobutane to provide **5_c**. As expected, the only workup needed for this reaction was filtration and concentration.

The choice of methods to arylate the oxazolidinone nitrogen is somewhat more difficult. While a few methods have been reported, the availability of the requisite aryl reagents (e.g., arylbismuth[19] and aryllead[20]) is not particularly good. Fortunately a method recently reported uses aryl bromides and the $Pd_2(dba)_3$/xantphos system to arylate amides.[21] This reaction appears to be quite general with most aryl bromides working well. We have used this method with all of our oxazolidinones and the aryl bromides shown in Scheme 4 to provide **5_a** and **5_b** in good yields. Workup for this reaction consisted of filtration through silica gel to provide pure product. Again, GC/MS and HPLC analysis of compounds **5aa**−**cc** showed them to be >82% pure. In general most of the compounds were >90% pure. Compounds **5ba** and **5ca** were of somewhat lower purity perhaps because of hydrolytic impurities of the ester and the somewhat basic reaction conditions.

The final step of the library generation is to functionalize position 5 (R^3) of the oxazolidinone ring. As shown in Scheme 5, we have used a reaction that converts a trityl ether to an ester in a single pot.[16] Each of the products from the

previous reaction, **5aa**−**5cc**, were treated with three different acid chlorides to provide products **6aaa**−**6ccc** (Table 2). The generality of this reaction has already been reported, the only limitation being the lack of reactivity of aryl acid chlorides. The workup for this reaction consisted of a base wash to remove excess acid chloride. The GC/MS and HPLC analysis confirmed that they were all >83% pure. Again, most of the compounds were significantly more pure, an average purity of 92.3%, with a few compounds, such as **6caa**, being recovered in lower purity perhaps because of the hydrolytic impurities of the ester and the somewhat acidic reaction conditions. The overall yields of the target oxazolidinones were generally excellent. Starting with 3.7 mmol of the bicyclic aziridine **3**, we isolated 2.55 mmol of product oxazolidinones, a 69% overall yield through three reactions.

We have shown that the bicyclic aziridine **3** is an excellent precursor for the parallel synthesis of multiply substituted oxazolidinones with defined stereochemistry. All of the reactions utilized in the synthesis of this demonstration library make use of reagents (Grignard reagents, aryl/alkyl bromide, and acid chlorides) that are widely available. We are currently preparing larger libraries of oxazolidinones, and we will report on the synthesis and biological assay of these compounds in due course.

Experimental Section

^{1}H NMR and ^{13}C NMR spectra were obtained on a Varian 250 MHz spectrometer. Unless otherwise noted, all spectra were recorded in $CDCl_3$ and referenced to TMS. GC/MS data were obtained using a CP SIL 8 column on a GCQ Finnagin MAT mass spectrometer. HPLC data were obtained using a SupelcoSil ABZ + Plus column (15 cm × 4.6 mm, 5 μm), eluting with 10% EtOAc/hexanes at 1 mL/min. Retention times are reported in minutes. Purification was done using flash chromatography on silica gel 60 (230−400 mesh). All reactions were carried out under an atmosphere of argon unless otherwise noted. All solvents were distilled before use. THF, dioxane, and Et_2O were distilled from sodium benzophenone ketyl. CH_2Cl_2 and PhH were distilled from CaH_2. DMF was distilled from BaO and stored over 3 Å molecular sieves. Grignard reagents and KF/Al_2O_3 were purchased from Aldrich Chemical Co. $Pd_2(dba)_3$ was purchased from Strem Chemicals.

1-(Triphenylmethoxy)-2-[(azidocarbonyl)oxy]-3-butene-(2). *CAUTION: Azides are potentially explosive, especially upon heating. While we have observed no problems with stability or formation of the azidoformates, care should be exercised.* Trityl ether **8** (3.14 g, 9.50 mmol) was dissolved in benzene (4.5 mL). Pyridine (2.3 mL, 28.5 mmol) and *p*-nitrophenyl chloroformate (3.83 g, 19.0 mmol) were added, and the reaction was stirred at room temperature for 4 h. The reaction mixture was diluted with EtOAc and washed with saturated $NaHCO_3$ (2×) and brine (2×), dried over $MgSO_4$, filtered, and concentrated. The crude product was then dissolved in DMF (64 mL), and NaN_3 (6.18 g, 95.0 mmol) was added. The reaction was heated to 35 °C and stirred for 18 h. The reaction mixture was diluted with EtOAc and washed with NH_4Cl (2×) and brine (2×), dried over $MgSO_4$, filtered, and concentrated. The product was chromatographed (2% EtOAc in hexanes), giving 2.98 g of **2** (79%) as a yellow oil. ^{1}H NMR: δ 1.2 (dt, J = 5.5, 3.25 Hz, 1 H), 1.6 (d, J = 4.0 Hz, 2 H), 4.0 (d, J = 6.0 Hz, 2 H), 4.2 (dt, J = 7.75, 4.5 Hz, 1 H), 7.2 (m, 15 H). ^{13}C NMR: δ 166.8, 143.6, 137.0, 128.5, 128.0, 127.3, 87.2, 72.0, 67.4. IR (CCl_4, cm^{-1}): 2112, 1734, 1672. Anal. Calcd for $C_{25}H_{21}O_3N_3$: C, 72.97; H, 5.19; N, 10.18. Found: C, 72.61; H, 5.58; N, 9.79.

(Triphenylmethoxymethyl)-3-oxa-1-azabicyclo[3.1.0]-hexan-2-one (3). *CAUTION: Reactions conducted in pressure tubes are potentially explosive and should be carried out behind a protective shield. While we have observed no problems, care should be exercised.* Azidoformate **2** (1.93 g, 4.83 mmol) and 2,6-di-*tert*-butyl-4-methylphenol (BHT, 0.11 g, 0.483 mmol) were dissolved in CH_2Cl_2 (40 mL) and placed in an Ace resealable sealed tube (catalog no. 8648-86). The tube was cooled to −78 °C, evacuated, sealed, and heated to 109 °C for 13 h. The tube was cooled to room temperature and opened, and the resulting precipitate was filtered to give 1.2 g of **3** (50%) as a white powder, mp 205−206 °C. ^{1}H NMR: δ 1.2 (dt, J = 5.5, 3.25 Hz, 1 H), 1.6 (d, J = 4.0 Hz, 2 H), 2.0 (d, J = 6.25 Hz, 2 H), 2.2 (dt, J = 8.0, 4.3 Hz, 1 H), 7.2 (m, 15 H). ^{13}C NMR: δ 166.8, 143.6, 128.5, 128.0, 127.3, 87.2, 63.9, 39.9, 34.7. IR (CCl_4, cm^{-1}): 1734. Anal. Calcd for $C_{25}H_{21}O_3N\cdot H_2O$: C, 74.78; H, 6.06; N, 3.49. Found: C, 74.90; H, 5.94; N, 3.67.

1-(Triphenylmethoxy)-3-buten-2-ol (8). 3-Butene-1,2-diol[16] (0.85 mL, 10 mmol) was dissolved in DMF (20 mL). Trityl chloride (3.35 g, 12 mmol), DMAP (0.123 g, 1.22 mmol), and Et_3N (3.36 mL, 19.97 mmol) were added, and the reaction mixture was stirred at room temperature for 24 h. The reaction mixture was diluted with CH_2Cl_2 and washed with H_2O, cold 1 M HCl, saturated $NaHCO_3$, H_2O, and brine, dried over $MgSO_4$, filtered, and concentrated to give 3.14 g of **8** (95%) as a yellow oil. ^{1}H NMR: δ 1.2 (dt, J = 5.5, 3.25 Hz, 1 H), 1.6 (d, J = 4.0 Hz, 2 H), 4.2 (s, 1 H), 3.0 (d, J = 6.25 Hz, 2 H), 3.2 (dt, J = 8.25, 4.25 Hz, 1 H), 7.2 (m, 15 H). ^{13}C NMR: δ 146.9, 143.7, 137.0, 128.6, 127.9, 127.2, 72.0, 67.4. Anal. Calcd for $C_{24}H_{22}O_2\cdot{}^1/_2H_2O$: C, 82.00; H, 6.49; N, 0. Found: C, 82.04; H, 6.76; N, 0. IR (CCl_4, cm^{-1}): 3398, 1672.

Preparation of 4a−c. CuCN (0.045 g, 0.498 mmol) was suspended in Et_2O (10 mL) and cooled to −30 °C. Grignard reagent (9.76 mmol) was added, and the reaction mixture was stirred at −30 °C for 10 min. Oxazolidinone **3** (0.437 g, 1.22 mmol) was added, and the reaction mixture was warmed to 0 °C and stirred for 3 h. The flask was warmed to room temperature and the contents stirred for an additional 3 h. A pH 9 solution of NH_4OH/NH_4Cl was added, and the reaction mixture was extracted with EtOAc (2×), washed with water (2×) and brine (2×), dried over $MgSO_4$, filtered, and concentrated to give the desired products **4a**−**c** as yellow oils.

4a (Phenyl). ^{1}H NMR: δ 1.8 (dd, J = 4, 7.75 Hz, 2 H), 2.2 (d, J = 8.25 Hz, 2 H), 2.6 (d, J = 10.5 Hz, 2 H), 3.0 (s, 1 H), 7.2 (m, 15 H), 7.6 (m, 5 H). GC/MS, room temp: 5.55 min; M^+ 450 (MW 450.253). LC, retention time: 3.202 min, 84.3%.

Table 1

compd	MW (M^+)	weight (mg)	purity[a] (%)
5aa	584.263 (584)	187.6	88.2
5ab	556.548 (556)	209.4	92.2
5ac	506.387 (506)	404.6	84.6
5ba	612.398 (612)	165.5	81.5
5bb	585.003 (584)	196.3	92.3
5bc	534.268 (534)	460.3	98.1
5ca	589.746 (589)	123.4	78.1
5cb	561.248 (561)	115.5	87.7
5cc	511.612 (511)	153.7	96.0[b]

[a] Purity was based on the integration of the major peak of the HPLC trace. [b] Purity was based on GC integration.

4b (Phenethyl). ^{1}H NMR: δ 1.8 (dd, J = 4, 7.75 Hz, 2 H), 2.0 (d, J = 5.25 Hz, 2H), 2.2 (d, J = 8.25 Hz, 2 H), 2.6 (d, J = 10.5 Hz, 2 H), 3.0 (s, 1 H), 7.2 (m, 15 H), 7.6 (m, 5 H). GC/MS, retention time: 4.83 min; M^+ 478 (MW 478.846). LC, retention time: 3.167 min, 97.4%.

4c (Cyclohexyl). ^{1}H NMR: δ 1.6 (m, 11H), 1.8 (dd, J = 4, 7.75 Hz, 2 H), 2.2 (d, J = 8.25 Hz, 2 H), 2.6 (d, J = 10.5 Hz, 2 H), 3.0 (s, 1 H), 7.2 (m, 15 H). GC/MS, retention time: 2.14 min; M^+ 455 (MW 455.679). LC, retention time: 2.047 min, 77.0%.

Preparation of 5aa−5cc. The crude oxazolidinones **4a−c** were partitioned into nine equal portions (~0.4 mmol).

For alkylation, oxazolidinone **4a−c** was dissolved in THF (8 mL). KF/Al_2O_3 (738 mg of 40 wt %, 5.08 mmol, ground to a fine powder) and bromobutane (0.04 mL, 0.42 mmol) were added. The reaction mixture was stirred rapidly at room temperature for 24 h. The reaction mixture was filtered and concentrated to give the desired products **5_c** as yellow oils.

For arylation, $Pd_2(dba)_3$ (3.2 mg, 0.0035 mmol), xantphos[22] (6.36 mg, 0.011 mmol), $CsCO_3$ (159 mg, 0.489 mmol), and oxazolidinones **4a−c** were mixed in dioxane (2 mL), the aryl bromide (0.839 mmol) was added, and the reaction was heated to 100 °C for 48 h. The reaction mixture was concentrated and dissolved in 25% EtOAc in hexanes solution and applied to a prepackaged silica gel microcolumn and filtered to remove the unreacted material. The column was washed with 100% EtOAc to collect desired products **5_a** and **5_b**. Upon concentration, the products were obtained as a yellow oil (see Table 1 for analytical data). Representive ^{1}H NMR data (**5aa** and **5ac**) are listed below.

5aa. ^{1}H NMR: δ 1.4 (s, 3 H), 1.8 (dd, J = 4, 7.75 Hz, 2 H), 2.2 (d, J = 8.25 Hz, 2 H), 2.6 (d, J = 10.75 Hz, 2 H), 7.6 (m, 5 H), 7.8 (m, 15 H), 8.2 (m, 4 H).

5ac. ^{1}H NMR: δ 1.2 (m, 7 H), 1.6 (t, J = 5.25 Hz, 2 H), 1.8 (dd, J = 4, 7.75 Hz, 2 H), 2.2 (d, J = 8.25 Hz, 2 H), 2.6 (d, J = 10.75 Hz, 2 H), 7.6 (m, 5 H), 7.8 (m, 15 H).

Preparation of 6aaa−6ccc. The oxazolidinones **5aa−5cc** were dissolved in CH_2Cl_2 (3 mL) and cooled to 0 °C. Phenylacetyl chloride, cyclohexane carbonyl chloride, or octanoyl chloride (0.8 mmol, 200 mol %) was added, and the reaction mixture was stirred at room temperature for 24 h. The reaction mixture was washed with saturated $NaHCO_3$, H_2O, and brine, dried over $MgSO_4$, filtered, and concentrated to give the desired products **6aaa−6ccc** as a yellow oil (see Table 2 for analytical data). Representive ^{1}H NMR data are listed below.

Table 2

compd	MW (M^+)	weight (mg)	purity[a] (%)
6aaa	459.265 (459)	32.1	86.5
6aab	451.415 (451)	22.5	93.2
6aac	468.479 (468)	37.4	89.4
6aba	431.687 (431)	42.0	88.2
6abb	424.168 (424)	48.8	93.7
6abc	440.947 (440)	45.9	86.6
6aca	381.647 (381)	82.5	99.2
6acb	372.264 (372)	82.7	99.7
6acc	390.486 (390)	77.1	90.1
6baa	448.549 (448)	27.6	94.8
6bab	479.164 (479)	37.5	95.4
6bac	496.347 (496)	36.8	93.6
6bba	460.187 (460)	39.2	98.0
6bbb	452.379 (452)	46.6	87.0
6bbc	462.439 (462)	42.1	86.0
6bca	410.024 (410)	44.3	99.3
6bcb	402.103 (402)	82.5	89.0
6bcc	418.761 (418)	79.4	90.4
6caa	466.176 (466)	29.8	83.2
6cab	458.243 (458)	24.3	99.3
6cac	474.276 (474)	26.7	92.3
6cba	438.416 (438)	28.7	83.5
6cbb	430.135 (430)	25.2	99.0
6cbc	446.715 (446)	25.1	89.4
6cca	388.621 (388)	36.9	85.6
6ccb	380.048 (380)	28.6	99.2[b]
6ccc	396.164 (396)	34.7	99.4[b]

[a] Purity was based on the integration of the major peak of the HPLC trace. [b] Purity was based on GC integration.

6aaa. ^{1}H NMR: δ 1.0 (s, 3 H), 1.8 (dd, J = 4,7.75 Hz, 2 H), 2.2 (d, J = 8.25 Hz, 2 H), 2.2 (d, J = 10.75 Hz, 2 H), 3.4 (s, 2 H), 6.8 (m, 5 H), 7.0 (m, 5 H), 7.4 (m, 4 H).

6abb. ^{1}H NMR: δ 1.4 (s, 3 H), 1.6 (dd, J = 4, 7.75 Hz, 2 H), 2.0 (d, J = 8.25 Hz, 2 H), 2.4 (m, 10 H), 3.0 (d, J = 10.0 Hz, 2 H), 3.2 (q, J = 4.75 Hz, 1H), 7.0 (m, 5 H), 7.4 (m, 4 H).

6acc. ^{1}H NMR: δ 1.0 (m, 9 H), 1.2 (m, 15 H), 1.8 (dd, J = 4, 7.75 Hz, 2 H), 2.2 (d, J = 10.75 Hz, 2 H), 2.6 (d, J = 10.75 Hz, 2 H), 7.0 (m, 4 H).

6baa. ^{1}H NMR: δ 1.2 (s, 3 H), 1.4 (m, 4 H), 2.2 (d, J = 7.25 Hz, 2 H), 2.6 (d, J = 10.25 Hz, 2 H), 7.0 (m, 5 H), 7.2 (m, 5 H), 7.4 (m, 4 H).

6bbb. ^{1}H NMR: δ 1.2 (m, 4 H), 1.8 (m, 11 H), 2.0 (d, J = 7.0 Hz, 2 H), 2.2 (d, J = 9.75 Hz, 2 H), 7.0 (m, 5 H), 7.2 (m, 4 H).

6cbc. ^{1}H NMR: δ 1.0 (m, 15 H), 1.2 (s, 3 H), 1.6 (m, 11 H), 1.8 (d, J = 4 Hz, 2 H), 2.2 (d, J = 8 Hz, 2 H), 2.4 (d, J = 9.75 Hz, 2 H), 7.2 (m, 4 H).

6ccb. ^{1}H NMR: δ 1.0 (m, 9H), 1.1 (m, 10H), 1.2 (m, 11H), 1.8 (dd, J = 4, 7.5 Hz, 2H), 2.2 (d, J = 10.5 Hz, 2H), 2.6 (d, J = 10.5 Hz, 2H).

6ccc. ^{1}H NMR: δ 1.0 (m, 9H), 1.1 (m, 10H), 1.2 (m, 15H), 1.8 (dd, J = 4, 7.75 Hz, 2H), 2.2 (d, J = 10.75 Hz, 2H), 2.6 (d, J = 10.75 Hz, 2H).

Acknowledgment. We acknowledge the Office of the Vice President for Research for a Research Challenge Award to support this work. We gratefully acknowledge the Donors of the Petroleum Research Fund, administered by the

American Chemical Society for partial support of this work (Grant 31875-G1). We also thank Dr. D. M. Stanchina and Mr. K. M. Arason for early work on this project.

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