Design and Synthesis of Conformationally Constrained Analogues of 4-(3-Butoxy-4-methoxybenzyl)imidazolidin-2-one (Ro 20-1724) as Potent Inhibitors of cAMP-Specific Phosphodiesterase

Marcus F. Brackeen,*,† David J. Cowan,† Jeffrey A. Stafford,† Frank J. Schoenen,† James M. Veal,§ Paul L. Domanico,‡ Dudley Rose,‡ Alan B. Strickland,⊥ Margrith Verghese,⊥ and Paul L. Feldman†

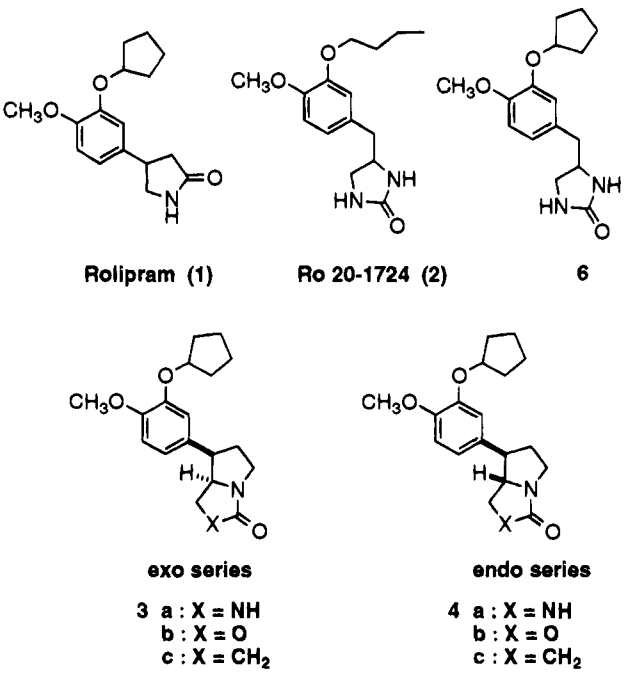
Glaxo Wellcome Research, Five Moore Drive, Research Triangle Park, North Carolina 27709

Received June 30, 1995®

The synthesis and biological evaluation of cAMP-specific phosphodiesterase (PDE IV) inhibitors is described. The PDE IV inhibitor 4-(3-butoxy-4-methoxybenzyl)imidazolidin-2-one (Ro 20-1724, **2**) was used as a template from which to design a set of rigid oxazolidinones, imidazolidinones, and pyrrolizidinones that mimic Ro 20-1724 but differ in the orientation of the carbonyl group. The endo isomer of each of these heterocycles was more potent than the exo isomer in an enzyme inhibition assay and a cellular assay, which measured TNFα secretion from activated human peripheral blood monocytes (HPBM). Imidazolidinone **4a** inhibited human PDE IV with a K_i of 27 nM and TNFα secretion from HPBM with an IC_{50} of 290 nM. By comparison, Ro 20-1724 is significantly less active in these assays with activities of 1930 and 1800 nM, respectively.

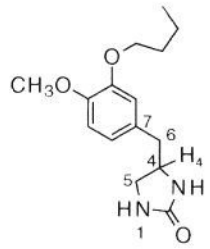
At least seven different gene families (isotypes) of cyclic nucleotide phosphodiesterases (PDE's) are known to catalyze the hydrolysis of 3′,5′-cyclic nucleotides, generating the corresponding 5′-nucleotide metabolites.[1] Of these gene families, type IV PDE, characterized as the cAMP-specific gene family, has been shown to predominate in proinflammatory human lymphoid and myeloid lineage cells.[2] It has been demonstrated that increasing cAMP levels within these cells results in suppression of cell activation which in turn inhibits the production and release of proinflammatory cytokines.[3] Within the past few years, much effort has been focused on identifying and validating PDE IV as a target for therapeutic intervention in inflammatory diseases such as rheumatoid arthritis and asthma, since these gene products regulate intracellular cAMP levels. Type IV selective phosphodiesterase inhibitors such as rolipram [(*R*,*S*)-4-[3-(cyclopentyloxy)-4-methoxyphenyl]-2-pyrrolidinone, **1**][4] and the less potent Ro 20-1724 (**2**)[5] have for many years served as useful tools for medicinal chemists in guiding their search for more potent and selective inhibitors of these enzymes with the ultimate goal of obtaining compounds which could be useful in treating inflammatory diseases.[6] In this paper we describe the synthesis and biological evaluation of a series of conformationally constrained analogues (**3**, **4**) of the selective PDE IV inhibitors rolipram (**1**) and Ro 20-1724 (**2**).

Although Ro 20-1724 and rolipram are structurally similar in their aromatic and heterocyclic compositions, rolipram is severalfold more potent at inhibiting PDE IV than Ro 20-1724. We reasoned that perhaps the decreased activity of Ro 20-1724 is, in part, due to its preference for one of three possible conformations (Figure 1), wherein the carbonyl group in a low-energy conformation cannot interact with the PDE enzyme as effectively as the lactam carbonyl of rolipram. Ro 20-1724 has two freely rotatable bonds, and rotation about the C4–C6 bond, in particular, yields three low-energy conformations characterized by the C7 atom of the aromatic ring being either trans to C5 (**2a**), trans to N1 (**2b**), or trans to H4 (**2c**). MM3 energy calculations[7] predict **2a** to be 0.9 kcal/mol lower in energy relative to the other two conformers. The energy difference appears to arise from several factors, one of which is the lack of steric hindrance between the C5 protons of the cyclic urea and the aromatic ring. Overlapping of the three conformers of Ro 20-1724 onto rolipram[8] demonstrates that conformer **2b** has significantly better overlap of the catechol ether ring and the urea carbonyl group than the other two conformers (Figure 2). We thus sought to synthesize analogues of Ro 20-1724 which would mimic this higher energy conformer (**2b**). When the benzylic carbon atom of **6** is appended to the proximal nitrogen of the heterocyclic ring with an ethylene linker, molecular modeling shows that one of



† Department of Medicinal Chemistry.
‡ Department of Biochemistry.
§ Department of Molecular Sciences.
⊥ Department of Cell Biology.
® Abstract published in *Advance ACS Abstracts*, October 15, 1995.

0022-2623/95/1838-4848$09.00/0



2

2 a **2 b** **2 c**

Figure 1. Three energy-minimized Ro 20-1724 conformations.

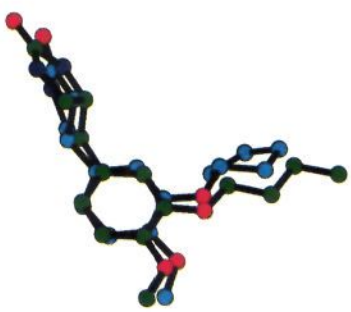


Figure 2. Overlay of **2b** and rolipram.

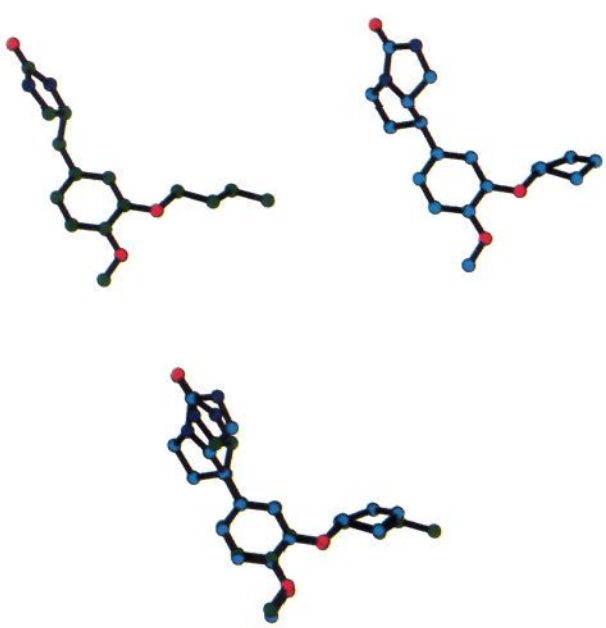


Figure 3. Overlay of **4a** and **2b**.

the generated diastereomers, **4a**, overlaps well with conformer **2b** (Figure 3) in contrast to the alternative diastereomer **3a**, which does not show significant overlap.[9] We therefore prepared **4a** and **3a** for comparison of PDE IV activity relative to both **1** and **2**. Additionally, we extended this study by preparing and testing the oxazolidinones **3b** and **4b** and the pyrrolizidinones **3c** and **4c**. Finally, we elected to append the rolipram aromatic nucleus to all of these analogues in order to allow base-line comparison to rolipram and the 3-(cyclopentyloxy)aryl analogue of Ro 20-1724, **6**.[10,11]

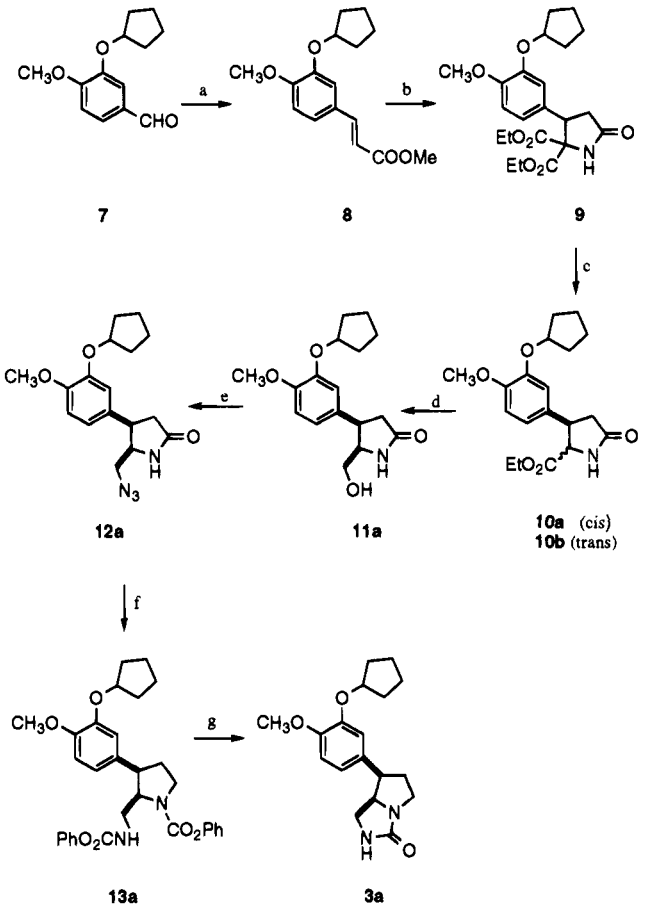
Chemistry

Imidazolidinones. The synthesis of the imidazolidinones **3a** and **4a** is shown in Scheme 1. Horner–Emmons homologation of aldehyde **7** yielded cinnamate **8** which in one step was transformed to the 5,5-bis(ethoxycarbonyl)pyrrolidinone **9** following a literature procedure.[12] Reaction of **9** with LiI and DMF generated a 1:1 mixture of diastereomers **10a,b**.[13,14] These isomers were separated, and the cis isomer **10a** was then reduced with $LiBH_4$ in THF to give alcohol **11a**. Mesylation of **11a** and displacement of the mesylate with sodium azide gave azide **12a**. Reduction of **12a** gave the corresponding diamine which was peracylated with phenyl chloroformate to afford **13a**. The bis-carbamate **13a** was refluxed in the presence of a 2-fold excess of sodium hydride in THF containing phenol, to deliver the imidazolidinone **3a**. The imidazolidinone **4a** was synthesized from **10b** using the same sequence of reactions used to prepare **3a**.

Oxazolidinones. The synthesis of oxazolidinone **3b** commenced with a reduction of lactam **10a** with $LiAlH_4$ (Scheme 2). The amino alcohol **16a** thus obtained was acylated with phenyl chloroformate to give the corresponding carbamate **17a**, which was subsequently exposed to NaH in THF to deliver the oxazolidinone **3b**. The endo diastereomer **4b** was synthesized in an analogous fashion beginning with **10b**.

Pyrrolizidinones. The synthesis of the pyrrolizidinones **3c** and **4c** is shown in Scheme 3. Aldehyde **7** was transformed to the dibromo olefin **18**. Treatment of **18** with *n*-butyllithium (THF, −78 °C), using the procedure of Corey and Fuchs, gave the terminal acetylene **19**.[15]

Scheme 1[a]



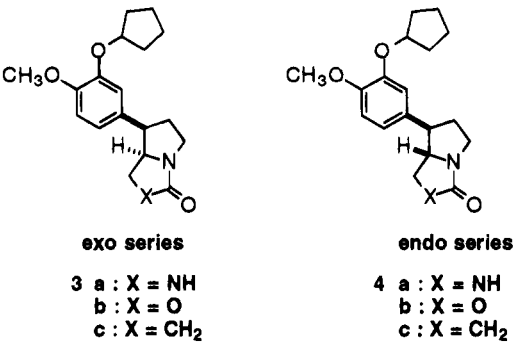
[a] Reactions and conditions: (a) $(CH_3O)_2POCH_2CO_2CH_3$, LHMDS, THF; (b) Na/EtOH, $(EtO_2C)_2CHNHCOCH_3$; (c) LiI, DMF, 100 °C; (d) $LiBH_4$, THF; (e) i. $ClSO_2CH_3$, Et_3N, DCM, ii. NaN_3, DMF, 50 °C; (f) i. LAH, THF, ii. $ClCO_2Ph$, Et_3N, THF; (g) NaH, PhOH, THF.

Regioselective hydrostannylation of **19** was accomplished by reaction with tributyltin hydride and catalytic tris(triphenylphosphine)rhodium(I) chloride.[16] The product **20** was treated with 3-carbomethoxypropionyl chloride in 1,2-dichloroethane in the presence of *trans*-benzyl(chloro)bis(triphenylphosphine)palladium(II) to give the ketone **21**.[17] Conjugate addition of nitromethane into the double bond then gave **22**, which upon treatment with Raney nickel underwent a tandem reduction–double cyclization to deliver the pyrrolizidinones **3c** and **4c** as a 2:1 (exo:endo) mixture of diastereomers. The diastereomers were readily separated using silica gel chromatography.

Biology

All of the compounds in Table 1 were tested for their ability to inhibit cAMP hydrolysis of the human PDE IV protein termed PDE type IVb.[18] This protein was recently cloned from a human frontal cortex cDNA library, expressed in the yeast *Saccharomyces cerevisiae*, and purified to functional homogeneity.[19] In order to assess the functional effects of these representative PDE IV inhibitors, they were tested for their ability to inhibit the production of tumor necrosis factor-α (TNF-α) from lipopolysaccharide (LPS)-stimulated human peripheral blood monocytes (HPBM) and mouse peritoneal macrophages.[20]

Table 1. Enzyme Inhibition Data and Chemical Properties of PDE IV Inhibitors **3a–c**, **4a–c**, and **6**



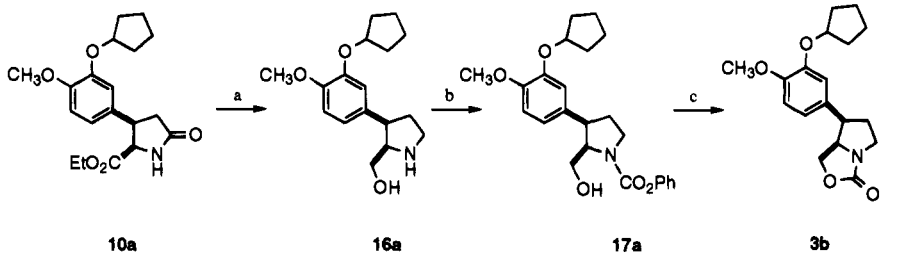
entry[a]	K_i (nM)[b]	±SD[c]	n[d]	formula[e]	mp (°C)
4a	27	1	3	$C_{18}H_{24}N_2O_3$	118–120
4b	70	10	3	$C_{18}H_{23}NO_4$	97–98
4c	63	26	4	$C_{19}H_{25}NO_3$	64–66
3a	583	110	3	$C_{18}H_{24}N_2O_3$	oil
3b	282	45	3	$C_{18}H_{23}NO_4$	89–91
3c	338	49	3	$C_{19}H_{25}NO_3$	78–80
1 (rolipram)	221	27	9	$C_{16}H_{21}NO_3$	131–133
2 (Ro 20–1724)	1930	425	4	$C_{15}H_{22}N_2O_3$	126
6	447	170	4	$C_{16}H_{22}N_2O_3$	101–103

[a] All compounds are racemic. [b] The K_i's of compounds set forth in the table were determined by measuring the inhibition of cAMP hydrolysis as a function of the concentration of the test compound over the range of 0.5 nM-100 μM. [c] SD is the standard deviation of the mean. [d] n is the number of experiments. [e] Analytical data for all compounds (C, H, N analyses) are within ±0.4% of the theoretical values.

Results and Discussion

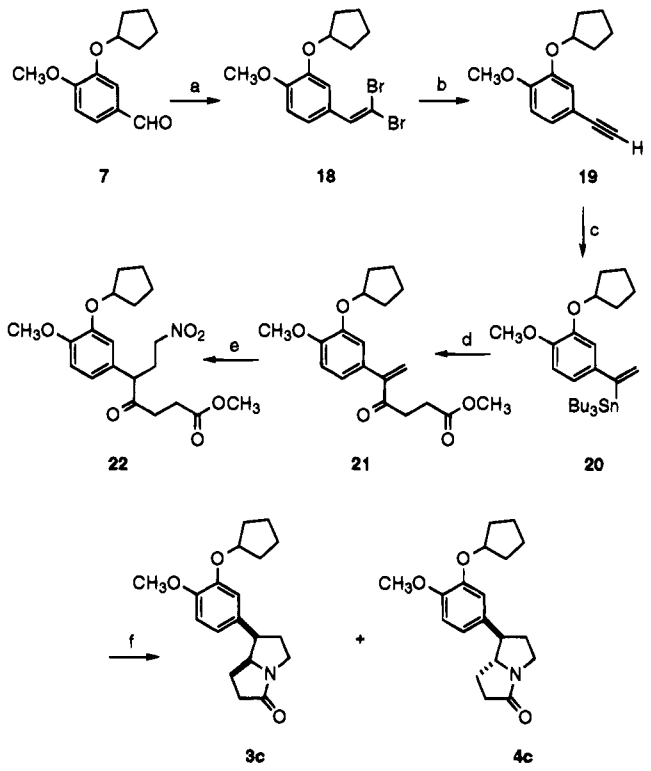
PDE IV inhibition data are shown in Table 1. As predicted from modeling, compounds **4a–c** demonstrated greater potency than their respective diastereomers **3a–c**. Variation among the ring CH_2, NH, or O did not show a significant impact on the compound's ability to inhibit the enzyme. Due to the observation that the entire endo series is much more potent than the entire exo series, and that the potency differences within each series are relatively small, we suggest that

Scheme 2[a]



[a] Reactions and conditions: (a) LAH, THF; (b) $ClCO_2Ph$, Et_3N, THF; (c) NaH, THF.

Scheme 3[a]



[a] Reactions and conditions: (a) PPh_3, CBr_4; (b) nBuLi, THF; (c) $RhCl(PPh_3)_3$, nBu_3SnH, THF; (d) *trans*-Bn(Cl)Pd(PPh_3)$_2$, DCE, $MeO_2C(CH_2)_2COCl$; (e) CH_3NO_2, TMG; (f) H_2, Ra-Ni.

the direction of the carbonyl oxygen influences enzyme inhibition more than a hydrogen bond donor (NH) or acceptor (O). As discussed above, we calculated that the Ro 20-1724 conformers **2b,c** are ca. 0.9 kcal/mol higher in energy than conformer **2a**. The data in Table 1 lend support to this calculation. One would expect that by constraining Ro 20-1724 to a single higher energy, yet presumably bioactive conformer **2b**, that the enthalpic and entropic energy costs required for Ro 20-1724 to adopt its active conformation are recovered in the form of binding affinity, i.e., enzyme inhibition. Comparing entries **4a** and **6**, which both contain the rolipram aromatic nucleus, we observe an ca. 16-fold increase in enzyme inhibition. A 16-fold increase in binding corresponds to a ~1.7 kcal/mol increase in binding free energy. Given the nature of the approximations used in this study, this result is consistent with the predicted conformational energy effects.

The more active diastereomer from each structural class was shown to be very selective for inhibition of PDE IV versus six other known PDE isotypes.[21] Furthermore, the most active compound from this series, **4a**, was tested for its ability to inhibit LPS-induced TNF-α secretion from purified HPBM. This compound demonstrated functional activity with an IC_{50} of 290 nM, comparable to rolipram, which has an IC_{50} of 320 nM in the same assay (cf. Ro 20-1724 with an IC_{50} of 1800 nM).[22]

Conclusion

In summary, we have synthesized a new class of PDE IV selective inhibitors based on the prototype inhibitors rolipram and Ro 20-1724. We believe that we have identified the active conformation of Ro 20-1724 by constraining it to a higher energy conformer. All three of the bicyclic compounds **4a–c** patterned after the active Ro 20-1724 conformer demonstrate significantly enhanced potency (<100 nM) at inhibiting PDE IV relative to Ro 20-1724 and should be useful tools for the future design of PDE IV inhibitors.

Experimental Section

Unless otherwise noted all starting materials were obtained from commercial suppliers and used without further purification. All reactions involving oxygen- or moisture-sensitive compounds were performed under a dry N_2 atmosphere. All reaction mixtures and chromatography fractions were analyzed by thin-layer chromatography on 250 mm silica gel plates and visualized with UV light and I_2 statin. Flash column chromatography was carried out using Merck silica gel 60 (230–400 mesh). ^1H NMR spectra were measured in $CDCl_3$ using either a Varian VXZ-300 or a Varian Unity-300 instrument. J values are reported in hertz. Chemical shifts are expressed in ppm downfield from internal tetramethylsilane. Apparent multiplicities are designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; b, broad. All mass spectra were taken in the positive ion mode under electrospray ionization (ESI), chemical ionization (CI), electron impact (EI), or fast-atom bombardment (FAB). Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Elemental analyses were performed by Atlantic Microlab, Norcross, GA.

3-(Cyclopentyloxy)-4-methoxybenzaldehyde (7). To a 2 L 2-neck flask were added sequentially 3-hydroxy-4-methoxybenzaldehyde (150 g, 986 mmol), potassium carbonate (204.4 g, 1.48 mol), and cyclopentyl bromide (191 g, 1.28 mol) in 1.0 L of DMF. The mixture was mechanically stirred at 65 °C for 16 h, cooled, and filtered and the filter cake washed with ethyl acetate. The filtrate was diluted with a 1:1 hexane: ethyl acetate solution and washed with water. The organic layer was extracted, dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give 215.3 g (99%) of **7** as an orange oil: ^1H NMR ($CDCl_3$) δ 9.83 (s, 1), 7.40 (m, 2), 6.97 (d, 1), 4.84 (m, 1), 3.91 (s, 3), 1.98–1.61 (m, 8).

***(E)*-Methyl-3-[3-(cyclopentyloxy)-4-methoxyphenyl]-prop-2-enoate (8).** To a solution of trimethyl phosphonoacetate (13 mL, 82 mmol) in 36 mL of THF at 0 °C was added lithium bis(trimethylsilyl)amide (82 mL of 1 M THF solution, 82 mmol). This solution was stirred for 20 min, and a solution of **7** (15 g, 68 mmol) in 30 mL of THF was then added dropwise via addition funnel. When reaction was judged complete by TLC analysis, the reaction mixture was diluted with ethyl acetate:hexanes (1:1), and the organic layer was washed with H_2O and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford 17.2 g (92%) of **8** as a pale yellow solid: ^1H NMR (300 MHz): δ 3.79 (s, 3), 3.86 (s, 3), 6.28 (d, 1, J = 16), 7.52 (d, 1, J = 16).

3-[3-(Cyclopentyloxy)-4-methoxyphenyl]-5-oxopyrrolidine-2,2-dicarboxylic Acid Diethyl Ester (9). To a solution of 75 mL of ethanol containing sodium (1.25 g, 54.3 mmol) was added diethyl acetamidomalonate (29.5 g, 136 mmol) followed by **8** (30.0 g, 108.6 mmol). The solution was refluxed for 48 h, cooled to room temperature, and then concentrated under reduced pressure to an oil. The oil was dissolved in ether, washed with cold 1 N sodium hydroxide (2×), and then concentrated under reduced pressure to an oil. The oil was then dissolved in a 20% solution of ethyl acetate in hexanes and allowed to stand at room temperature where crystallization occurred. The crystals were filtered and washed with ether to provide 12.92 g (28%) of **9** as a white solid: mp 127–129 °C; ^1H NMR (300 MHz) δ 0.87 (t, 3, J = 7.2), 1.27 (t, 3, J = 7.2), 1.57–1.94 (m, 8), 2.56 (dd, 1, J = 17.4, 3), 2.91 (dd, 1, J = 17.1, 8.7), 3.63–3.74 (m, 1), 3.79 (s, 3), 3.81–3.91 (m, 1), 4.20–4.35 (m, 3), 4.68–4.73 (m, 1), 6.61 (s, 1), 6.73–6.80 (m, 3).

***cis/trans*-3-[3-(Cyclopentyloxy)-4-methoxyphenyl]-5-oxopyrrolidine-2-carboxylic Acid Ethyl Ester (10a,b).** To a solution of **9** (12.0 g, 28.63 mmol) in DMF was added lithium

iodide (12.0 g, 89.7 mmol). The resulting suspension was heated at 100 °C for 3 h and then cooled to room temperature. The solution was diluted with 500 mL of H_2O, extracted with ethyl acetate (2×), washed with water (3×) and brine, dried ($MgSO_4$), filtered, and concentrated to a 1:1 mixture of diastereomers as an oil. The mixture was chromatographed on silica gel to provide 4.4 g (44%) of the less polar diastereomer **10b** as a colorless oil: ^1H NMR (300 MHz) δ 1.24 (t, 3, J = 7.5), 1.57–1.91 (m, 8), 2.49 (dd, 1, J = 17.4, 6.9), 2.83 (dd, 1, J = 17.1, 9.3), 3.58–3.66 (m, 1), 3.82 (s, 3), 4.12–4.25 (m, 3), 4.72–4.78 (m, 1), 6.78–6.81 (m, 4).

Further elution provided 3.3 g (33%) of the more polar diastereomer **10a** as a white solid: mp 109–110 °C; ^1H NMR (300 MHz) δ 0.89 (t, 3, J = 7.5), 1.57–1.94 (m, 8), 2.70 (dd, 2, J = 8.4, 2.1), 3.66–3.85 (m, 1), 3.79 (s, 3), 3.88 (q, 2, J = 7.8), 4.53 (d, 2), 4.69–4.73 (m, 1), 6.63 (s, 1), 6.72–6.78 (m, 3).

***cis*-4-[3-(Cyclopentyloxy)-4-methoxyphenyl]-5-(hydroxymethyl)pyrrolidin-2-one (11a).** To a solution of **10a** (4.75 g, 13.69 mmol) in 50 mL of THF was added $LiBH_4$ (500 mg, 23.8 mmol) in portions. The resultant suspension was stirred at room temperature for 2 h and then chilled to 0 °C. The solution was then successively treated dropwise with methanol (10 mL), H_2O (10 mL), and 1 M H_3PO_4 (50 mL). The resulting solution was extracted with ethyl acetate (2×), washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give 2.35 g (55%) of **11a** as a solid: mp 143–145 °C; ^1H NMR (300 MHz) δ 1.59–1.81 (m, 8), 2.54–2.75 (m, 2), 3.10–3.26 (m, 2), 3.71–3.75 (m, 1), 3.77 (s, 3), 3.86–3.89 (m, 1), 4.75–4.80 (m, 1), 6.76–6.88 (m, 3).

***trans*-4-[3-(Cyclopentyloxy)-4-methoxyphenyl]-5-(hydroxymethyl)pyrrolidin-2-one (11b):** prepared following the procedure described above for **11a** to give **11b** as a solid; mp 132–133 °C. Anal. Calcd for $C_{17}H_{23}NO_4$: C, 66.9; H, 7.5; N, 4.6. Found: C, 66.8; H, 7.6; N, 4.6.

***cis*-5-(Azidomethyl)-4-[3-(cyclopentyloxy)-4-methoxyphenyl]pyrrolidin-2-one (12a).** To a solution of **11a** (2.1 g, 6.87 mmol) in 20 mL of CH_2Cl_2 at 0 °C was added triethylamine (1.1 mL, 7.56 mmol) followed by dropwise addition of methanesulfonyl chloride (585 mL, 7.56 mmol). The resulting solution was stirred for 6 h and then diluted with 1 M H_3PO_4 (100 mL), extracted with ethyl acetate (2×), washed with brine, dried ($MgSO_4$), filtered, and concentrated to an oily residue which was chromatographed on silica gel (2:1, hexanes: ethyl acetate) to give 2.1 g (85%) of the corresponding mesylate. The mesylate (1.6 g, 4.55 mmol) and sodium azide (1.0 g, 15.38 mmol) in 10 mL of DMF were heated at 85 °C for 2.5 h. The resulting solution was cooled to room temperature and then diluted with ethyl acetate and poured into 1 M H_3PO_4. The aqueous layer was extracted with ethyl acetate (2×), washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Silica gel chromatography (3:1 hexanes: ethyl acetate) gave 1.11 g (73%) of **12a** as an oil: ^1H NMR (300 MHz) δ 1.53–1.93 (m, 8), 2.56–2.75 (m, 2), 2.89–3.10 (m, 2), 3.72–3.94 (m, 2), 3.79 (s, 3), 4.70–4.74 (m, 1), 6.69–6.81 (m, 3), 7.38 (s, 1).

***trans*-5-(Azidomethyl)-4-[3-(cyclopentyloxy)-4-methoxyphenyl]pyrrolidin-2-one (12b):** prepared following the procedure described above for **12a** to give **12b** as an oil. Anal. Calcd for $C_{17}H_{22}N_4O_3$: C, 61.8; H, 6.7; N, 17.0. Found: C, 62.1; H, 6.9; N, 16.8.

***cis*-3-[3-(Cyclopentyloxy)-4-methoxyphenyl]-2-[[*N*-(phenoxycarbonyl)amino]methyl]pyrrolidine-1-carboxylic Acid Phenyl Ester (13a).** To a suspension of **12a** (3.3 g, 9.96 mmol) in 60 mL of THF at 0 °C was added $LiAlH_4$ (30 mL, 30 mmol, 1 M THF solution) dropwise. The resultant solution was stirred, refluxed for 3 h, and then cooled at room temperature. The solution was then successively treated dropwise with H_2O (1.1 mL), 15% NaOH (1.1 mL), and H_2O (3.3 mL). The resulting suspension was stirred for 1 h, diluted with ether, filtered through Celite, and concentrated under reduced pressure to give *cis*-2-(aminomethyl)-3-[3-(cyclopentyloxy)-4-methoxyphenyl]pyrrolidine as an oil (2.85 g, 98%). To a solution of this diamine (2.1 g, 7.23 mmol) in 20 mL of THF at 0 °C was added 4-methylmorpholine (1.6 mL, 14.5 mmol) followed by dropwise addition of phenyl chloroformate (1.81 mL, 14.5 mmol). The ice bath was removed and the resulting suspension stirred at room temperature for 30 min and then diluted with ethyl acetate and poured into 1 M H_3PO_4. The aqueous layer was extracted with ethyl acetate (2×), washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Silica gel chromatography (8:2 hexanes:ethyl acetate) gave 2.2 g (57%) of **13a** as an oil: ^1H NMR (300 MHz) δ 1.59–1.92 (m, 8), 2.27–2.32 (m, 1), 2.41–2.52 (m, 1), 2.96–3.91 (m, 4), 3.84 (s, 3), 4.27–4.53 (m, 2), 4.77–4.79 (m, 1), 6.05 (bs, 1), 6.77–7.41 (m, 13).

***trans*-3-[3-(Cyclopentyloxy)-4-methoxyphenyl]-2-[[*N*-(phenoxycarbonyl)amino]methyl]pyrrolidine-1-carboxylic acid phenyl ester (13b):** prepared following the procedure described above for **13a** to give **13b** as an oil; ^1H NMR (300 MHz) δ 1.58–1.91 (m, 8), 2.20–2.24 (m, 2), 3.54–3.66 (m, 4), 3.84 (s, 3), 4.03–4.08 (m, 1), 4.29–4.38 (m, 1), 4.78–4.79 (m, 1), 6.28 (bs, 1), 6.79–7.40 (m, 13).

***exo*-7-[3-(Cyclopentyloxy)-4-methoxyphenyl]hexahydropyrrolo[1,2-*c*]imidazol-3-one (3a).** To a solution of **13a** (2 g, 3.78 mmol) in 40 mL of THF at 0 °C was added NaH (160 mg, 4.0 mmol, 60% oil dispersion). The mixture was stirred for 15 min, and additional NaH (260 mg, 6.5 mmol) was added followed by dropwise addition of a solution of phenol (500 mg, 5.31 mmol) in 5 mL of THF. The resulting solution was refluxed for 30 min, cooled to room temperature, and then diluted with ethyl acetate and poured into 1 M H_3PO_4. The aqueous layer was extracted with ethyl acetate (2×), washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Silica gel chromatography (95:5 CH_2Cl_2: methanol) gave 700 mg (59%) of **3a** as an oil which crystallized on standing: ^1H NMR (300 MHz) δ 1.53–1.89 (m, 8), 1.98–2.1 (m, 1), 2.21–2.33 (m, 1), 2.82–2.86 (m, 1), 3.1–3.4 (m, 4), 3.77 (s, 3), 4.67–4.71 (m, 1), 5.1 (bs, 1), 6.51–6.75 (m, 3). Anal. Calcd for $C_{18}H_{24}N_2O_3$: C, 68.3; H, 7.7; N, 8.9. Found: C, 68.3; H, 7.7; N, 8.8.

***endo*-7-[3-(Cyclopentyloxy)-4-methoxyphenyl]hexahydropyrrolo[1,2-*c*]imidazol-3-one (4a):** prepared following the procedure described above for **3a** to give **4a** as a solid; mp 118–120 °C; ^1H NMR (300 MHz) d 1.58–1.91 (m, 8), 1.98–2.12 (m, 1), 2.31–2.41 (m, 1), 2.69–2.78 (m, 1), 3.28–3.74 (m, 5), 3.82 (s, 3), 4.73–4.79 (m, 1), 5.61 (bs, 1), 6.72–6.84 (m, 3); ^{13}C NMR (300 MHz) δ 23.9, 32.7, 34.3, 41.2, 45.1, 48.4, 56.1, 66.1, 80.5, 112.2, 114.5, 119.5, 131.6, 147.9, 149.3, 165.9. Anal. Calcd for $C_{18}H_{24}N_2O_3$: C, 68.3; H, 7.7; N, 8.9. Found: C, 68.3; H, 7.7; N, 8.8.

***cis*-3-[3-(Cyclopentyloxy)-4-methoxyphenyl]pyrrolidine-2-methanol (16a).** To a solution of **10a** (500 mg, 1.4 mmol) in 20 mL of THF at 0 °C was added $LiAlH_4$ (2.88 mL, 2.88 mmol, 1 M THF solution) dropwise. The resultant solution was stirred and refluxed for 2 h and then cooled to room temperature. The solution was then successively treated dropwise with H_2O (0.10 mL), 15% NaOH (0.10 mL), and H_2O (0.30 mL). The resulting suspension was stirred for 1 h, diluted with ether, filtered through Celite, and concentrated under reduced pressure to give 390 mg (93%) of **16a**. Anal. Calcd for $C_{17}H_{25}NO_3$: C, 70.1; H, 8.7; N, 4.8. Found: C, 70.1; H, 7.1; N, 3.4.

***cis*-3-[3-(Cyclopentyloxy)-4-methoxyphenyl]pyrrolidine-2-methanol (16b):** prepared following the procedure described above for **16a** to give **16b** as an oil. Anal. Calcd for $C_{17}H_{25}NO_3$: C, 70.1; H, 8.7; N, 4.8. Found: C, 70.1; H, 7.1; N, 3.4.

***cis*-3-[3-(Cyclopentyloxy)-4-methoxyphenyl]-2-(hydroxymethyl)pyrrolidine-1-carboxylic Acid Phenyl Ester (17a).** To a solution of **16a** (271 mg, 1.0 mmol) in 7 mL of CH_2Cl_2 at 0 °C was added TEA (275 μL, 1.9 mmol) followed by dropwise addition of phenyl chloroformate (137 μL, 1.1 mmol). The ice bath was removed and the resulting suspension stirred at room temperature for 30 min and then diluted with ethyl acetate and poured into 10 mL of 1 M H_3PO_4. The aqueous layer was extracted with ethyl acetate (2×), washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Silica gel chromatography (8:2 hexanes: ethyl acetate) gave 219 mg (51%) of **17a**. Anal. Calcd for $C_{24}H_{29}NO_5$: C, 70.1; H, 7.1; N, 3.4. Found: C, 70.0; H, 7.1; N, 3.4.

***trans*-3-[3-(Cyclopentyloxy)-4-methoxyphenyl]-2-(hydroxymethyl)pyrrolidine-1-carboxylic acid phenyl ester**

(**17b**): prepared following the procedure described above for **17a** to give **17b** as an oil. Anal. Calcd for $C_{24}H_{29}NO_5$: C, 70.1; H, 7.1; N, 3.4. Found: C, 70.0; H, 7.1; N, 3.4.

***exo*-7-[3-(Cyclopentyloxy)-4-methoxyphenyl]tetrahydropyrrolo[1,2-*c*]oxazol-3-one (3b).** To a solution of **17a** (219 mg, 0.53 mmol) in 10 mL of THF was added NaH (50 mg, 1.25 mmol). The resulting suspension was stirred for 2 h, diluted with 10 mL of 1 M H_3PO_4, and then extracted with ethyl acetate. The organics were washed with water (2×), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give 145 mg (89%) of **3b** which slowly crystallized on standing: mp 89–91 °C; ^{1}H NMR (300 MHz) δ 1.59–1.94 (m, 8), 2.15–2.25 (m, 1), 2.33–2.48 (m, 1), 3.25–3.35 (m, 2), 3.71 (dd, 1, J = 8.4, 3), 3.79 (s, 3), 3.86–3.95 (m, 1), 4.14–4.28 (m, 2), 4.69–4.74 (m, 1), 6.47–6.54 (m, 2), 6.78 (d, 1, J = 8.4). Anal. Calcd for $C_{18}H_{23}NO_4$: C, 68.1; H, 7.3; N, 4.4. Found: C, 67.9; H, 7.3; N, 4.4.

***endo*-7-[3-(Cyclopentyloxy)-4-methoxyphenyl]tetrahydropyrrolo[1,2-*c*]oxazol-3-one (4b):** prepared following the procedure described above for **3b** to give **4b** which slowly crystallized on standing: mp 97–98 °C; ^{1}H NMR (300 MHz) d 1.54–1.95 (m, 8), 2.04–2.20 (m, 1), 2.41–2.51 (m, 1), 2.72–2.82 (m, 1), 3.41–3.49 (m, 1), 3.66–3.75 (m, 1), 3.80 (s, 3), 4.18 (dd, 1, J = 9.3, 3), 4.39 (dd, 1, J = 9, 7.5), 4.72–4.78 (m, 1), 6.71–6.73 (m, 2), 6.82 (d, 1, J = 8.1). Anal. Calcd for $C_{18}H_{23}NO_4$: C, 68.1; H, 7.3; N, 4.4. Found: C, 68.0; H, 7.4; N, 4.4.

2-(Cyclopentyloxy)-4-(2,2-dibromovinyl)-1-methoxybenzene (18). To a 2 L 2-neck flask was added carbon tetrabromide (165.6 g, 499.4 mmol) in 500 mL of dry CH_2Cl_2. While stirring with a mechanical stirrer at 0 °C, triphenylphosphine (262 g, 998.7 mmol) was added slowly in four portions over ca. 30 min. The ice bath was then removed, and an addition funnel charged with 3-(cyclopentyloxy)-4-methoxybenzaldehyde (55 g, 249.7 mmol) in 500 mL of dry CH_2Cl_2 was attached. The aldehyde solution was slowly added to the phosphoranylidene suspension at room temperature. After the addition was complete, the reaction mixture was filtered. The filtrate was concentrated, dissolved in 1:1 hexane:ethyl acetate, filtered twice through Celite, and concentrated to give 80 g (85%) of **18** as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 7.39 (s, 1), 7.22 (s, 1), 7.02 (d, 1), 6.83 (d, 1), 4.76 (m, 1), 3.85 (s, 3), 1.95–1.61 (m, 8).

2-(Cyclopentyloxy)-4-ethynyl-1-methoxybenzene (19). To a 1.0 M THF solution of 2-(cyclopentyloxy)-4-(2,2-dibromovinyl)-1-methoxybenzene (65 g, 172.8 mmol) at −78 °C was slowly added a 2.5 M solution of *n*-butyllithium (141.7 mL, 354.3 mmol) in THF over a 30 min period under N_2. This solution was stirred an additional 25 min, then the reaction was quenched with saturated NH_4Cl, and the mixture was warmed to room temperature and diluted with ether. The organic layer was washed with H_2O and brine, dried ($MgSO_4$), filtered, and concentrated to give 35.5 g (95%) of **19** as a white solid: ^{1}H NMR ($CDCl_3$) δ 7.06 (d, 1), 6.99 (s, 1), 6.79 (d, 1), 4.75 (m, 1), 3.83 (s, 3), 2.99 (s, 1), 1.95–1.59 (m, 8).

2-(Cyclopentyloxy)-1-methoxy-4-[1-(tributylstannyl)-vinyl]benzene (20). To a solution of **19** (10 g, 46.2 mmol) in 50 mL of THF was added tris(triphenylphosphine)rhodium(I) chloride (0.41 g, 0.44 mmol). Tributyltin hydride (11.8 mL, 44.0 mmol) was added to the stirring mixture at room temperature, and the solution was allowed to stir for an additional 1.5 h. The solvent was removed under reduced pressure, and the residue was dissolved in 90:10 hexane;ethyl acetate and filtered through Celite to remove the catalyst. The filtrate was concentrated and chromatographed on silica gel (95:5 hexane:ethyl acetate) to give 20.7 g (92.4%) of **20** as a pale yellow oil: ^{1}H NMR ($CDCl_3$) δ 6.79–6.74 (m, 3), 6.00 (d, 1, J = 2.4), 5.33 (d, 1, J = 2.4), 4.77 (m, 1), 3.83 (s, 3), 1.93–1.60 (m, 8), 1.46–0.85 (m, 27).

5-[3-(Cyclopentyloxy)-4-methoxyphenyl]-4-oxohex-5-enoic Acid Methyl Ester (21). To a 100 mL 2-neck flask were added sequentially **20** (4.25 g, 8.38 mmol) in 20 mL of 1,2-dichloroethane, 3-carbomethoxypropionyl chloride (0.94 mL, 7.6 mmol), and *trans*-benzyl(chloro)bis(triphenylphosphine)palladium(II) (0.12 g, 0.15 mmol). The solution was heated for 16 h at 85 °C. The solution was then cooled and filtered through Celite. The filtrate was concentrated and chromatographed on silica gel (3:1 hexane:ethyl acetate) to give 1.36 g (49%) of **21** as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 6.86–6.83 (m, 3), 6.04 (s, 1), 5.83 (s, 1), 4.76 (m, 1), 3.82 (s, 3), 3.66 (s, 3), 3.04 (t, 2), 2.65 (t, 2), 1.90–1.58 (m, 8).

5-[3-(Cyclopentyloxy)-4-methoxyphenyl]-7-nitro-4-oxoheptanoic Acid Methyl Ester (22). To a solution of **21** (1.36 g, 4.09 mmol) in 20 mL of nitromethane was added tetramethylguanidine (257 μL, 2.04 mmol). This solution was then heated to 85 °C while stirring for 2 h and then cooled. The solution was concentrated under reduced pressure to a reddish brown residue which was chromatographed on silica gel (75:25 hexane:ethyl acetate) to give 1.35 g (84%) of **22** as an orange oil: ^{1}H NMR ($CDCl_3$) δ 6.84 (d, 1), 6.70–6.61 (m, 2), 4.74 (m, 1), 4.30 (m, 2), 3.83 (s, 3), 3.73 (m, 1), 3.64 (s, 3), 2.75–2.59 (m, 4), 2.45 (m, 1), 2.30 (m, 1), 1.95–1.61 (m, 8).

7-[3-(Cyclopentyloxy)-4-methoxyphenyl]hexahydropyrrolizidin-3-one (3c, 4c). To a 340 mL capacity sealed pressure reactor equipped with a mechanical stirrer were added a solution of **22** (1.35 g, 3.43 mmol) in 100 mL of methanol and W-2 grade Raney nickel (1.0 g). The vessel was sealed, evacuated under reduced pressure, and then pressurized to 80 psi with hydrogen. The reaction mixture was stirred and heated at 65 °C for 6 h and then cooled. The solution was filtered through Celite and concentrated to a pale yellow oil. The residue was chromatographed on silica gel (95:5 ether:hexane) to provide 280 mg (26%) of the less polar diastereomer **3c**: mp 78–80 °C; ^{1}H NMR ($CDCl_3$) δ 6.76 (d, 1), 6.50–6.45 (m, 2), 4.71 (m, 1), 4.16 (m, 1), 3.80 (m, 4), 3.18 (m, 2), 2.48 (m, 2), 2.27 (m, 1), 2.02–1.38 (m, 11). Anal. Calcd for $C_{19}H_{25}NO_3$: C, 72.4; H, 8.0; N, 4.4. Found: C, 71.9; H, 8.0; N, 4.4.

Further elution provided 600 mg (55%) of the more polar diastereomer **4c**: mp 64–66 °C; ^{1}H NMR ($CDCl_3$) δ 6.83 (d, 1), 6.75 (m, 2), 4.76 (m, 1), 3.91–3.81 (m, 4), 3.62 (m, 1), 3.32 (m, 1), 2.80–2.63 (m, 2), 2.52 (m, 2), 2.27 (m, 2), 1.91–1.60 (m, 9). Anal. Calcd for $C_{19}H_{25}NO_3$: C, 72.4; H, 8.0; N, 4.4. Found: C, 71.9; H, 8.0; N, 4.4.

Acknowledgment. We would like to thank Drs. Vince Florio, Kerry Fowler, Kate Loughney, and Tim Martins of the ICOS Corp., Dr. Graeme Bolger of the University of Utah, Bart Steiner and Lothar Uher of ICOS, and Dr. Peter J. Brown of Glaxo Wellcome for advice and reagents.

References

(1) Beavo, J. A.; Conti, M.; Heaslip, R. J. Multiple Cyclic Nucleotide Phosphodiesterases. *Mol. Pharmacol.* **1994**, *46*, 399–405.

(2) Robicsek, S. A.; Blanchard, D. K.; Djeu, J. Y.; Kranowski, J. J.; Szentivanyi, A.; Polson, J. B. Multiple high-affinity cAMP-phosphodiesterases in human T-lymphocytes. *Biochem. Pharmaco.* **1991**, *42*, 869–877.

(3) Verghese, M. W.; Snyderman, R. Signal transduction and intracellular messengers. In *Human monocytes*; Zembala, M., Asherson, G. L., Eds.; Academic Press Ltd.: London, 1989; pp 101–112.

(4) Schwabe, U.; Miyake, M.; Ohga, Y.; Daly, J. 4-(3-Cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidone (ZK 62711): A potent inhibitor of adenosine cyclic 3′,5′-monophosphate phosphodiesterase in homogenates and tissue slices from rat brain. *Mol. Pharmacol.* **1976**, 900–910.

(5) Gruenman, V.; Hoffer, M. 4-Benzyl-2-imidazolidinones from N-[(1-cyano-2-phenyl)ethyl]carbamates. U.S. Patent 3,923,833.

(6) (a) Marivet, M. C.; Bourguignon, J.-J.; Lugnier, C.; Mann, A.; Stoclet, J.-C.; Wermuth, C.-G. Inhibition of cyclic adenosine-3′,5′-monophosphate phosphodiesterase from vascular smooth muscle by rolipram analogues. *J. Med. Chem.* **1989**, *32*, 1450–1457. (b) Koe, B. K.; Lebel, L. A.; Nielsen, J. A.; Russo, L. L.; Saccomano, N. A.; Vinick, F. J.; Williams, I. H. Effects of novel catechol ether imidazolidonones on calcium-independent phosphodiesterase activity, [^{3}H]rolipram binding, and reserpine-induced hypothermia in mice. *Drug Dev. Res.* **1990**, *21*, 135–142. (c) Pinto, I. L.; Buckle, D. R.; Readshaw, S. A.; Smith, D. G. The selective inhibition of phosphodiesterase IV by benzopyran derivatives of rolipram. *Biorg. Med. Chem. Lett.* **1993**, *3*, 1743–1746. (d) Baures, P. W.; Eggleston, D. S.; Erhard, K. F.; Cieslinski, L. B.; Torphy, T. J.; Christensen, S. B. The crystal structure, absolute configuration, and phosphodiesterase inhibitory activity of (+)-1-(4-bromobenzyl)-4-(3-(cyclopentyoxy)-4-methoxyphenyl-pyrrolidin-2-one. *J. Med. Chem.* **1993**, *36*, 3274–3277. (e) Ashton, M. J.; Cook, D. C.; Fenton, G.; Karlsson, J.-A.; Palfreyman, M. N.; Raeburn, D.; Ratcliff, A. J.; Souness, J.

E.; Thurairatnam, S.; Vicker, N. Selective type IV phosphodiesterase inhibitors as antiasthmatic agents. The syntheses and biological activities of 3-(cyclopentyloxy)-4-methoxybenzamides and analogues. *J. Med. Chem.* **1994**, *37*, 1696–1703. (f) Stafford, J. A.; Feldman, P. L.; Marron, B. E.; Schoenen, F. J.; Valvano, N. L.; Unwalla, R. J.; Domanico, P. L.; Brawley, E. S.; Leesnitzer, M. A.; Rose, D. A.; Dougherty, R. W. Structure-activity relationships involving the catechol subunit of rolipram. *Biorg. Med. Chem. Lett.* **1994**, *4*, 1855–1860.

(7) Allinger, N. L.; Yuh, Y. H.; Lii, J. H. Molecular Mechanics. The MM3 Force Field for Hydrocarbons. *J. Am. Chem. Soc.* **1989**, *111*, 8551–8566.

(8) The active conformation of (*R*)-(−)-rolipram has been the subject of recent debate. See, for example: (a) Marivet, M. C.; Bourguignon, J.-J.; Lugnier, C.; Mann, A.; Stoclet, J.-C.; Wermuth, C.-G. Inhibition of cyclic adenosine-3′,5′-monophosphate phosphodiesterase from vascular smooth muscle by rolipram analogues. (b) Baures, P. W.; Eggleston, D. S.; Erhard, K. F.; Cieslinski, L. B.; Torphy, T. J.; Christensen, S. B. *J. Med. Chem.* **1993**, *36*, 3274. The active (*R*)-(−)-rolipram conformation that we favor is that proposed by Marivet et al.

(9) The root mean square deviation (rmsd) between **2** and each of the diastereomers **4a** and **3a** was evaluated using the carbonyl group, the centroid of the aryl ring, and the two ether oxygens as reference points (five points total). **4a** showed a high degree of overlap (Figure 3) with rmsd = 0.14, while **3a**, in contrast, showed significantly worse overlap (rmsd = 1.01).

(10) Compound **6** was prepared from **7** using a known literature procedure; see: Gruenman, V.; Hoffer, M. 4-Benzyl-2-imidazolidinones from N-[(1-cyano-2-phenyl)ethyl]carbamates. U.S. Patent 3,923,833.

(11) The single modification of **2** to its cyclopentyl analogue **6** resulted in a 4-fold increase in potency (Table 1).

(12) Cocolas, G. H.; Hartung, W. H. Michael Addition Reactions of Diethyl Acetamidomalonate. *J. Org. Chem.* **1957**, *79*, 5203.

(13) McMurry, J. E.; Wong, G. B. *Synth. Commun.* **1972**, *2*, 389.

(14) The relative stereochemistry of diastereomers **10a,b**, respectively, was unequivocally determined by COSY and NOESY experiments.

(15) Corey, E. J.; Fuchs, P. L. A Synthetic Method For Formyl to Ethynyl Conversion. *Tetrahedron Lett.* **1972**, *36*, 3769–3772.

(16) Kikukawa, K.; Umekawa, H.; Wada, F.; Matsuda, T. Regioselective Hydrostannylation of Terminal Acetylenes under Transition Metal Catalysis. *Chem. Lett.* **1988**, 881–884.

(17) Ley, S. V.; Trudell, M. L.; Wadsworth, D. J. The Total Synthesis of Agglomerin A and (±)-Carolinic Acid. A General Method for the Preparation fo 3-Acyl Tetronic Acids Via Direct Acylation of O-Methyl 3-Stannyl Tetronates. *Tetrahedron* **1988**, *47*, 8285–8296.

(18) Bolger, G.; Michaeli, T.; Martins, T.; St. John, T.; Steiner, B.; Rodgers, L.; Riggs, M.; Wigler, M.; Ferguson, K. A family of human phosphodiesterases homologous to the Dunce learning and memory gene product of Drosophila melanogaster are potential targets for anti-depressant drugs. *Mol. Cell Biol.* **1993**, *13*, 6558–6571.

(19) McLaughlin, M. M.; Cieslinski, L. B.; Burman, M.; Torphy, T. J.; Livi, G. P. A low-K_m rolipram-sensitive, cAMP-specific phosphodiesterase from human brain. *J. Biol. Chem.* **1993**, *268*, 6470–6476.

(20) (a) Semmler, J. H.; Wachtel, H.; Endres, S. The specific type IV phosphodiesterase inhibitor rolipram suppresses tumor necrosis factor-α production by human mononuclear cells. *Int. J. Immunopharmacol.* **1993**, *15*, 409–413. (b) Molnar-Kimber, K. L.; Yonno, L.; Heaslip, R. J.; Weichman, B. M. Differential regulation of TNF-α and IL-1β production from endotoxin stimulated human monocytes by phosphodiesterase inhibitors. *Mediators Inflammation* **1992**, *1*, 411–417.

(21) Compounds **4a–c** demonstrated greater than 100-fold selectivity for inhibition of the PDE IV isotype (data not shown). The authors thank C. Bonk and M. Snowden (Glaxo Research Development, U.K.) for performing these experiments.

(22) For the protocol for this assay, see: Feldman, P. L.; Brackeen, M. F.; Cowan, D. J.; Marron, B. E.; Schoenen, F. J.; Stafford, J. A.; Suh, E. M.; Domanico, P. L.; Rose, D.; Leesnitzer, M. A.; Brawley, E. S.; Stickland, A. B.; Verghese, M. W.; Connolly, K. M.; Bateman-Fite, R.; Noel, L. S.; Sekut, L.; Stimpson, S. A. Phosphodiesterase Type IV Inhibition. Structure-Activity Relationships of 1,3-Disubstituted Pyrrolidines. *J. Med. Chem.* **1995**, *38*, 1505.

JM9504868