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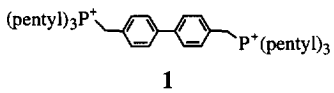
SYNTHESIS OF NON-PEPTIDE BRADYKININ B_2 RECEPTOR ANTAGONISTS

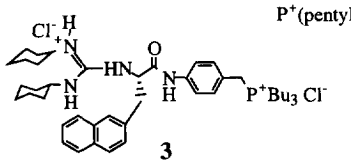
Brent D. Douty, Joseph M. Salvino,* Peter R. Seoane, and Roland E. Dolle
Department of Medicinal Chemistry
Sterling Winthrop Pharmaceutical Research Division, 1250 South Collegeville Road,
P.O. Box 5000, Collegeville Pennsylvania 19426-0900

Abstract: The syntheses of the potent, competitive bradykinin B_2 receptor antagonists, **1-3**, are described. These compounds represent the three structural classes of B_2 receptor antagonists discovered in our program. Compounds **1-3** bind to the human IMR 90 fetal lung fibroblast bradykinin B_2 receptor with affinity constants K_i = 3.4 μM, 0.77 μM, and 0.060 μM, respectively.

Antagonists of the bradykinin B_2 receptor have been suggested as potential therapeutic agents to treat pain and inflammation.[1] Recently we reported the design of non-peptide bradykinin B_2 receptor antagonists.[2] In the accompanying paper, the structure activity relationships of several classes of non-peptide antagonists are described.[3] These include the biphenyl bis-phosphonium, benzophenone bis-phosphonium and the amino acid phosphoniums, exemplified by **1-3**, respectively. In this paper we report our general synthetic route to these molecules by describing the syntheses of **1-3**.



1



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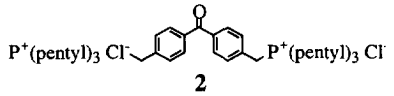
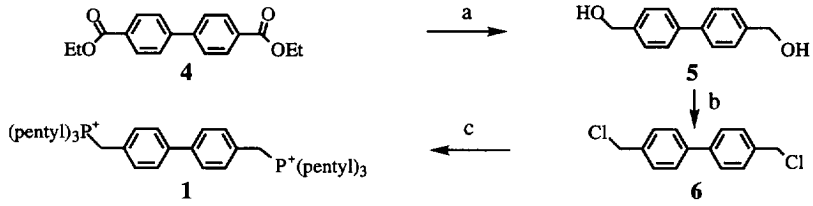


2

Analogs of the biphenyl bis-phosphonium series of antagonists, exemplified by compound **1**, were synthesized in a three step procedure outlined in Scheme 1. Thus, diethyl 4,4'-biphenyl dicarboxylate **4** was reduced by lithium aluminum hydride in THF to diol **5** in 91% yield. Diol **5** was subsequently converted to the bis-chloride by reaction with thionyl chloride in CH_2Cl_2 (97% yield). The bis-chloride **6** was a central intermediate from which a number of analogs were synthesized. For example, reaction of **6** with excess tripentyl phosphine in refluxing toluene resulted in the precipitation of **1**. Filtration, followed by washing with copious amounts of anhydrous diethyl ether provided analytically pure **1** as a white hygroscopic solid.[4]

Scheme 1[a]



[a]Key: (a) LAH, 2.0 equiv, THF, 0 °C→25 °C, 3 h, 91% (b) $SOCl_2$, 2.5 equiv, CH_2Cl_2, 25 °C, 6 h, 97 (c) $P(pentyl)_3$, 5.0 equiv, toluene, reflux, 24 h, 81%.

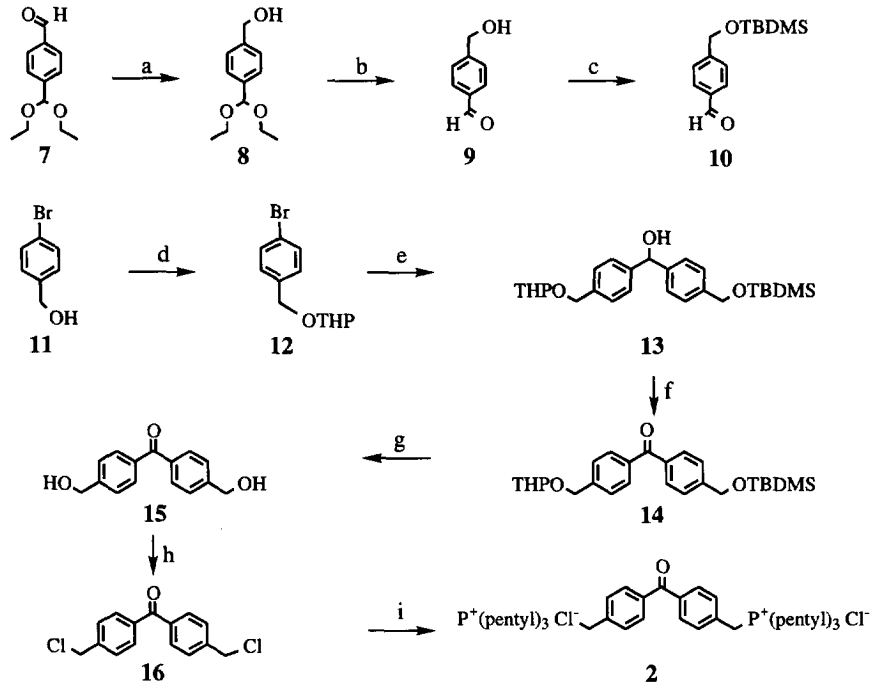
The benzophenone bisphosphonium class of antagonists was synthesized by coupling an appropriately functionalized aryl lithium reagent with a benzaldehyde derivative followed by oxidation and subsequent elaboration exemplified by **2** (Scheme 2). Accordingly, 4-(diethoxymethyl)benzaldehyde **7** was reduced to the alcohol **8** by the action of sodium borohydride in methanol at 0 °C for 1 h. Aqueous work-up followed by treatment with a catalytic amount of *p*-TsOH in THF for 1 h resulted in **9** as a white solid (80% isolated yield). Compound **9** was then protected as the *tert*-butyldimethyl silyl ether (92% yield) to give aldehyde **10**. Compound **12** was converted to the aryl lithium reagent by treatment with *sec*-butyl lithium at -78 °C. Aldehyde **10** was then added to this anion at -78 °C and the reaction mixture was allowed to warm to ambient temperature for 20 h. Work-up of the reaction followed by MnO_2 oxidation of the crude **13** in CH_2Cl_2 resulted in **14**. Purification by silica gel chromatography (25% ethyl acetate-hexanes) gave a 95% yield of **14** as a colorless oil. Treatment of **14** with a catalytic amount of pyridinium *p*-toluenesulphonate in absolute ethanol at 55 °C for 24 h resulted in the diol **15**. Chlorination[5] of **15** followed by silica gel chromatography (10% ethyl acetate-hexanes) gave pure dichloride **16** in 62% yield. Compound **16** was then combined with excess tripentyl phosphine (5.0 equiv) and heated at reflux in toluene overnight to generate the bis-phosphonium salt **2**. Filtration followed by washing with anhydrous diethyl ether and drying in a vacuum oven at 70 °C for 24 h gave **2** as a yellow hygroscopic solid.[6]

The amino acid based analogs, exemplified by the compound **3**, were the most potent bradykinin B_2 receptor antagonists discovered in our study. These molecules were arrived at using a linear five step procedure starting from the N-BOC protected amino acid. Thus for the synthesis of **3**, N-BOC-L-β-(2-naphthyl)alanine **17** was coupled to 4-aminobenzyl alcohol using BOP-Cl[7] in acetonitrile at 0 °C for 48 h. Purification by silica gel chromatography gave the coupled alcohol **18** (Scheme 3) in 46% yield. Conversion of the benzylic alcohol **18** to the benzylic chloride **19** was accomplished by treatment of **18** with methane sulphonyl chloride at 0 °C in DMF in the presence of collidine followed by the addition of excess lithium chloride. Aqueous work-up followed by silica gel chromatography gave **19** in 93% yield. Chloride **19** was then reacted with tributyl phosphine in refluxing toluene to produce the phosphonium salt **20** as a white precipitate which was isolated in 98% yield. Cleavage of the acid labile N-BOC protecting group by stirring with 3N HCl in THF for 12 h followed by removal of the solvent *in vacuo* gave **21**. The ammonium salt **21** was then combined with N,N'-dicyclohexyl carbodiimide in anhydrous acetonitrile and stirred at ambient temperature for 48 h. Removal of the solvent and trituration of the

residue with diethyl ether furnished **3**. Compound **3** was then washed several times with hot ethyl acetate to remove residual N,N'-cyclohexyl urea, and then dried at 45 °C under high vacuum to yield analytically pure material.[8]

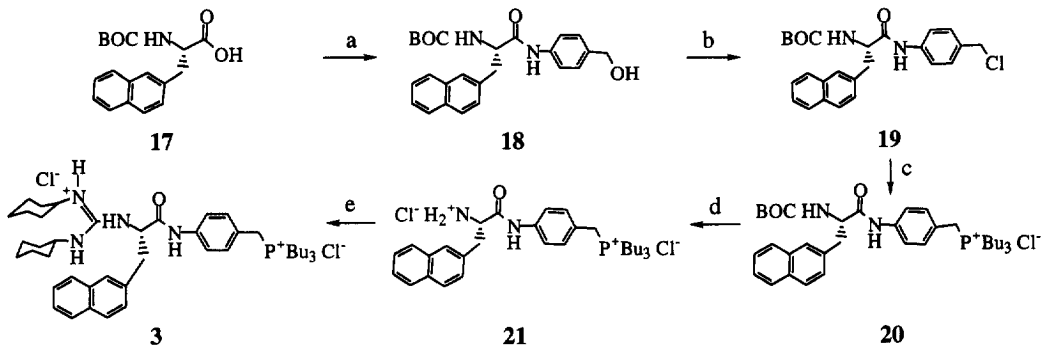
In conclusion, the syntheses of compounds **1-3** is reported herein. These molecules are non-peptide competitive antagonists of the human IMR 90 fetal lung fibroblast bradykinin B_2 receptor and bind with affinity constants K_i = 3.4 μM, 0.77 μM, and 0.060 μM, respectively. The synthetic routes developed for **1-3** were adapted to prepare a host of analogs in our bradykinin B_2 receptor antagonist program as described in the accompanying paper.[3]

Scheme 2[a]



[a]Key: (a) $NaBH_4$, 2.0 equiv, MeOH, 0 °C→25 °C, 1 h (b) TsOH, 0.1 equiv, THF, 25 °C, 1 h, 80% for the two steps. (c) *tert*-butyldimethylsilyl chloride, 1.2 equiv, imidazole, 2.5 equiv, DMF, 0 °C→25 °C, 3 h, 92% (d) dihydropyran, 1.1 equiv, PPTS, 0.1 eq., CH_2Cl_2, 25 °C, 18 h, 89% (e) sec-BuLi (1.45 M in cyclohexane), 1.3 equiv, THF, -78 °C, 30 min, then **10**, -78 °C→25 °C, 20 h (f) MnO_2, 10 equiv, CH_2Cl_2, 25 °C, 3 h, 95% for the two steps (g) PPTS, 0.2 equiv, EtOH, 55 °C, 24 h, 73% (h) MsCl, 2.2 equiv, collidine, 2.2 equiv, LiCl, 2.1 equiv., DMF, 6 h, 0 °C→25 °C, 72% (i) $P(pentyl)_3$, 5.0 equiv, toluene, reflux, 18 h, 85%.

Scheme 3[a]



[a]Key: (a) BOP-Cl, 1.5 equiv, CH_3CN, Et_3N, 3.0 equiv, 0 °C→25 °C, 30 min, then 4-amino-benzyl alcohol, 2.0 equiv, 25 °C, 48 h, 46% (b) MsCl, 1.5 equiv, collidine, 2.5 equiv, LiCl, 12 equiv, DMF, 0 °C→25 °C, 2.5 h, 93% (c) PBu_3, 5.0 equiv, Toluene, reflux, 8 h, 98% (d) 3 N HCl, THF, 25 °C, 12 h, 95% (e) DCC, 5.0 equiv, CH_3CN, 25 °C, 48 h, 90%.

References and Notes

1. a) Regoli, D.; Barabe, J. C. *J. Pharmacol. Rev.* **1980**, *32*, 1-46. b) Farmer, S. G.; Burch, R. M. *Bradykinin Antagonists: Basic and Clinical Research:* Burch, R. M., Ed.; Marcel Dekker: NY, 1990; pp 1-31.
2. Salvino, J. M.; Seoane, P. R.; Douty, B. D.; Awad, M. M. A.; Dolle, R. E.; Houck, W. T.; Faunce, D. M.; Sawutz, D. G. *J. Med. Chem.* **1993**, *36*, 2583-2584.
3. Salvino, J. M.; Seoane, P. R.; Douty, B. D.; Awad, M. M. A.; Hoyer, D.; Ross, T.; Dolle, R. E.; Houck, W. T.; Faunce, D. M.; Sawutz, D. G. *BioMed. Chem. Lett.,* manuscript submitted.
4. ^{1}H NMR of **1**: (300 MHz, DMSO-d_6) d 0.84 (18H, t, J = 6.6 Hz), 1.22-1.49 (36 H, m), 2.11-2.23 (12 H, m), 3.87 (4H, d, J = 15.9 Hz), 7.42 (4H, d, J = 8.1 Hz), 7.73 (4H, d, J = 7.7 Hz). CHN $C_{44}H_{78}P_2Cl{\cdot}1/2\ H_2O$ calc. %C = 70.56, %H = 10.63; found %C = 70.58, %H = 10.30.
5. Collington, E. W.; Meyer, A. I. *J. Org. Chem.* **1971**, *36*, 3044-3045.
6. ^{1}H NMR of **2**: (300 MHz, DMSO-d_6) δ 0.83 (18H, t, J = 7.2 Hz), 1.19 - 1.49 (36H, m), 2.18 - 2.29 (12H, m), 3.95 (4H, d, J = 16.1 Hz), 7.53 (4H, d, J = 6.2 Hz), 7.73 (4H, d, J = 8.1 Hz). CHN $C_{45}H_{78}Cl_2OP_2{\cdot}H_2O$ calc. %C = 68.76, %H = 10.26; found %C = 68.77, %H = 10.26
7. Diago-Meseguer, J.; Palomo-Coll, A. L.; Fernandez-Lizarbe, J. R.; Zugaza-Bibao, A. *Synthesis* **1980**, 547.
8. ^{1}H NMR of **3**:(300 MHz, DMSO-d_6) δ 0.87 (9H, t), 0.90-1.80(32H, m), 2.07 (6H, m), 3.20-3.40 (4H, m), 3.76 (2H, d, J = 15.26 Hz), 5.18 (1H, m), 7.20-7.95 (11H, m), 11.35 (s, 1H); CHN for $C_{45}H_{68}ON_4PCl{\cdot}HCl{\cdot}H_2O$ calc. %C = 67.40, %H = 8.92, %N = 6.99; found %C = 67.40, %H = 8.75, %N = 6.94 FAB mass spectrum *m/z* = 712 $[M - HCl - Cl^-]^+$

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