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Synthesis of a 2-Benzazepine Analog of a Potent, Nonpeptide GPIIb/IIIa Antagonist

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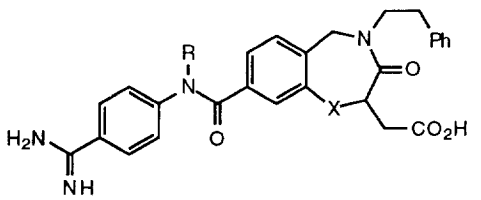
Abstract: The preparation of the 2-benzazepine derivative **3** as an analog of the potent, nonpeptide GPIIb/IIIa antagonist **2** is reported. The synthetic route employs as key steps a Heck arylation of dimethyl itaconate and a selective cyclization to form the aryl-fused seven-membered ring.

Platelet aggregation has been shown to be mediated, at least in part, by the GPIIb/IIIa receptor complex on the platelet plasma membrane surface.[1] This receptor, a member of the integrin superfamily of adhesion receptors, is known to recognize the Arg-Gly-Asp (RGD) tripeptide sequence. Aggregation occurs when fibrinogen, a natural ligand for GPIIb/IIIa which contains the RGD sequence, binds to GPIIb/IIIa on adjacent activated platelets. Disruption of this binding interaction has been demonstrated to inhibit platelet aggregation, and may provide a possible therapeutic approach to the treatment of thrombotic disorders, such as myocardial infarction and stroke.

Recently, we reported the direct design of 1,4-benzodiazepine **1** from a constrained peptide, and showed **1** to be a highly potent and selective GPIIb/IIIa antagonist.[2] In subsequent studies, we methylated the linking amide to afford 1,4-benzodiazepine **2**, which is comparable to **1** in binding affinity, but shows significant improvement both in inhibiting platelet aggregation and in oral bioavailability.[3] In order to investigate the contribution of N-1 to the binding, antiaggregatory, and oral activities of **2**, we prepared 2-benzazepine **3**, wherein N-1 of the 1,4-benzodiazepine nucleus has been replaced by a methylene group. In this communication, we describe the synthesis of compound **3**.

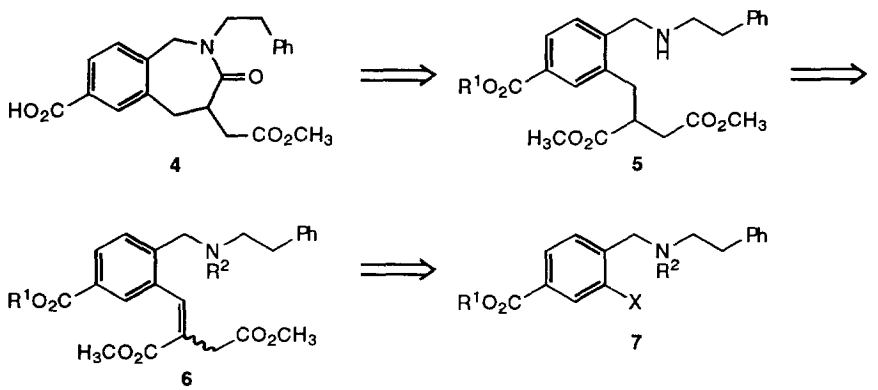


1 X = NH, R = H
2 X = NH, R = CH_3
3 X = CH_2, R = CH_3

Our general strategy[4] for the construction of the 2-benzazepine-4-acetic acid ring system is outlined in retrosynthetic fashion in Scheme 1. Based on our previous experience with the formation of the 1,4-benzodiazepine-2-acetic acid ring system,[2,3] we expected that amino diester **5** would cyclize to give the desired seven-membered ring-containing product rather than the undesired eight-membered ring-containing product. We reasoned that amino diester **5** might be available by appropriate manipulation of itaconate

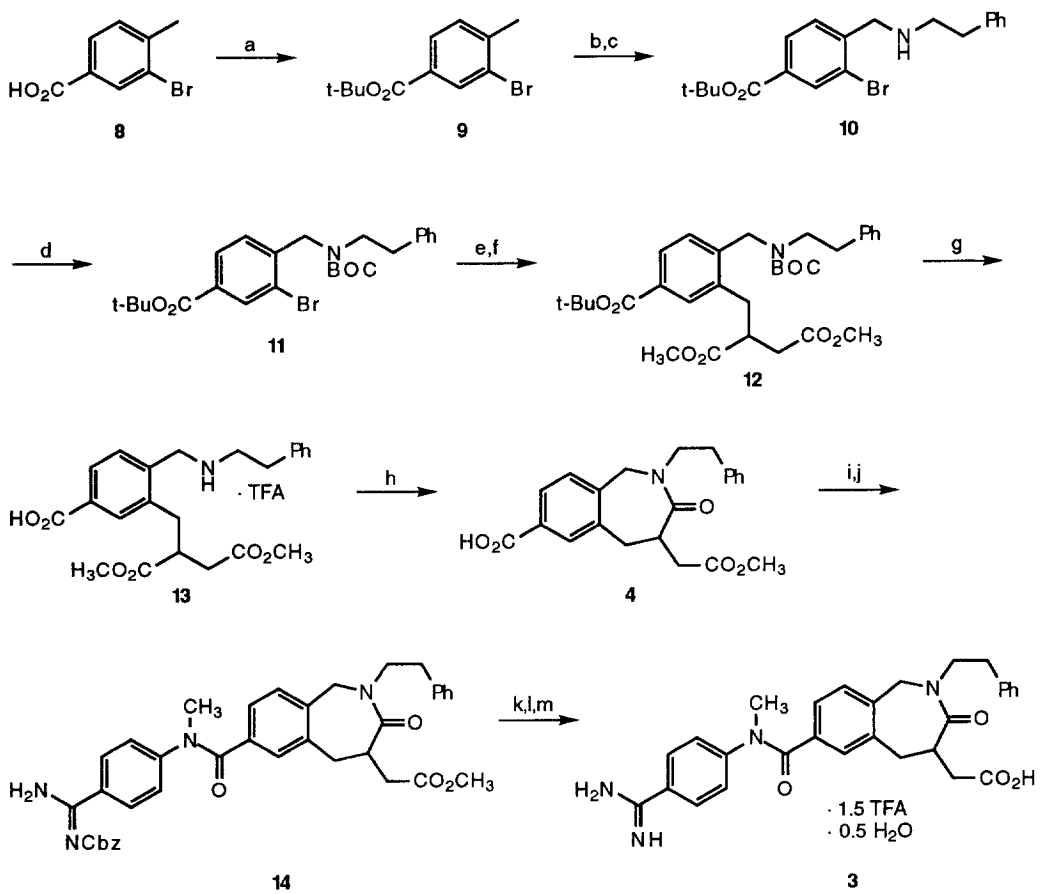
derivative **6**, which could, in principle, arise from a Heck reaction[5] between an aryl halide **7** (X = Br or I) and dimethyl itaconate.[6] This key carbon-carbon bond-forming reaction would establish in a single operation the remaining functionality required for the construction of benzazepine **4**.

Scheme 1



The synthesis of **3** began with commercially available 3-bromo-4-methylbenzoic acid (**8**), which was esterified with isobutylene in the presence of catalytic trifluoromethanesulfonic acid to afford *tert*-butyl 3-bromo-4-methylbenzoate (**9**) in 91% yield (Scheme 2).[7] Benzylic bromination with NBS, followed by reaction of the crude benzyl bromide with excess phenethylamine, gave amine **10** in 49% overall yield from **9**. The amino group was protected using di-*tert*-butyl dicarbonate, which produced BOC derivative **11** in quantitative yield. When an acetonitrile solution of **11**, dimethyl itaconate, 5 mole % $Pd(OAc)_2$, 10 mole % tri-*o*-tolylphosphine, and triethylamine was heated at reflux overnight, an isomeric mixture of the desired olefinic Heck products was produced. After removal of the tri-*o*-tolylphosphine and polar materials by flash chromatography on silica gel,[8] this mixture was hydrogenated over 10% palladium on carbon. Purification afforded succinate derivative **12** in 88% overall yield from aryl bromide **11**. The *tert*-butyl ester and *tert*-butylcarbamate protecting groups of **12** were removed simultaneously with trifluoroacetic acid (TFA) in CH_2Cl_2 to afford cyclization precursor **13** as its TFA salt in 93% yield. Without purification, **13** was cyclized in refluxing toluene in the presence of triethylamine to give methyl (±)-7-carboxy-3-oxo-2-(2-phenylethyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate (**4**) in 98% yield. Alternatively, **13** could be cyclized on exposure to NaOMe in refluxing methanol,[2] albeit in lower yield (72%). The 400 MHz ^1H NMR spectrum of **4**, on comparison with the ^1H NMR spectrum of the corresponding 1,4-benzodiazepine system,[3] fully supported the structural assignment. In particular, the benzylic amide protons of **4** appeared as an AX system, with one of the protons at δ 5.21 and the other at δ 3.84. The large difference in chemical shift for these protons appears to be characteristic of both the 1,4-benzodiazepine-2-acetic acid and 2-benzazepine-4-acetic acid ring systems. Unequivocal support for the structural assignment was obtained by single-crystal X-ray diffraction analysis, which confirmed the presence of the desired seven-membered ring.[9]

Scheme 2



a) isobutylene, 5 mole % TfOH, Et_2O, sealed pressure bottle, -78°C to RT (91%); b) NBS, $(PhCO_2)_2O$, CCl_4, reflux; c) $Ph(CH_2)_2NH_2$, THF, RT (49% from **9**); d) $(BOC)_2O$, $CHCl_3$, RT (quantitative); e) dimethyl itaconate, 5 mole % $Pd(OAc)_2$, 10 mole % P(*o*-tol)$_3$, Et_3N, CH_3CN, reflux; f) 50 psi H_2, 10% Pd/C, MeOH, RT (two times) (88% from **11**); g) 1:1 TFA/CH_2Cl_2, 0°C to RT (93%); h) Et_3N, toluene, reflux (98%); i) $SOCl_2$, reflux; j) 4-[N-(benzyloxycarbonyl)aminoiminomethyl]-N-methylaniline, pyridine, CH_2Cl_2, 0°C to RT (87% from **4**); k) 50 psi H_2, 10% Pd/C, 1:1 EtOAc/MeOH, RT; l) 1.0 N NaOH, MeOH, 0°C to RT; m) TFA, 1:1 CH_3CN/H_2O, 0°C (67% from **14**).

To complete the synthesis, benzazepine **4** was heated with thionyl chloride, and the putative acid chloride was reacted with 4-[N-(benzyloxycarbonyl)aminoiminomethyl]-N-methylaniline[3] to afford the coupling product **14** in 87 % yield. Hydrogenolysis of the Cbz group over 10 % palladium on carbon, saponification of the methyl ester with 1.0 N NaOH in methanol, acidification with TFA, and purification of the resulting material by reversed-phase flash chromatography provided the target compound **3** in 67 % yield from **14**.

In summary, we have synthesized the 2-benzazepine-4-acetic acid derivative **3** as an analog of the potent, nonpeptide GPIIb/IIIa antagonist **2**. The synthetic route incorporates as key operations a Heck reaction of aryl bromide **11** with dimethyl itaconate and a selective cyclization to form the seven-membered lactam ring. The results of biological testing of compound **3** and related analogs will be described in a forthcoming full account of this work.

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† Author to whom inquiries concerning the X-ray crystal structure analysis should be addressed.

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9. Tables of crystal data, fractional atomic coordinates, anisotropic thermal parameters for non-hydrogen atoms, bond distances and angles have been included with the deposited supplementary material sent to the Cambridge Crystallographic Data Centre, Lensfield Road, Cambridge CB2 1EW, United Kingdom. Listings of structure factors are available from the authors upon request.

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