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LETTERS

The synthesis of corticosteroid–carborane esters for the treatment of rheumatoid arthritis via boron neutron capture synovectomy

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Abstract

Two corticosteroid–carborane esters were synthesized through the use of a BOP-Cl promoted esterification. The steroid–carborane conjugates are designed to selectively deliver boron to arthritic tissue for boron neutron capture synovectomy, a new therapeutic approach for rheumatoid arthritis. © 2000 Elsevier Science Ltd. All rights reserved.

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Boron neutron capture therapy (BNCT) is a binary method for treating cancer that is currently undergoing clinical trials in several countries.[1] The interest in BNCT stems from the short path lengths of the reaction products of the $^{10}B[n,\alpha]\ ^{7}Li$ reaction. The damage caused by $^{7}Li^{3+}$ and $^{4}He^{2+}$ ions is limited to a distance that is approximately equal to the diameter of a single cell. For this reason, a great deal of effort has been spent designing boron-containing compounds that selectively target cancer cells rather than healthy ones.[2]

The application of the boron neutron capture reaction to treat diseases other than cancer has not received nearly as much attention, despite the potential for truly selective therapy. The use of the boron neutron capture reaction to treat arthritis, boron neutron capture synovectomy (BNCS), has been proposed recently as a new therapy modality for rheumatoid arthritis patients who do not respond to conventional drug therapy.[3,4] Our BNCS methodology involves administering a boron-containing species directly into the arthritic joint prior to irradiation with thermal neutrons.[5] Once inside the appropriate tissue, the fission products from the boron neutron capture reaction are sufficiently energetic to irreparably damage the affected cells thereby affording relief to the patient. The key to the success of

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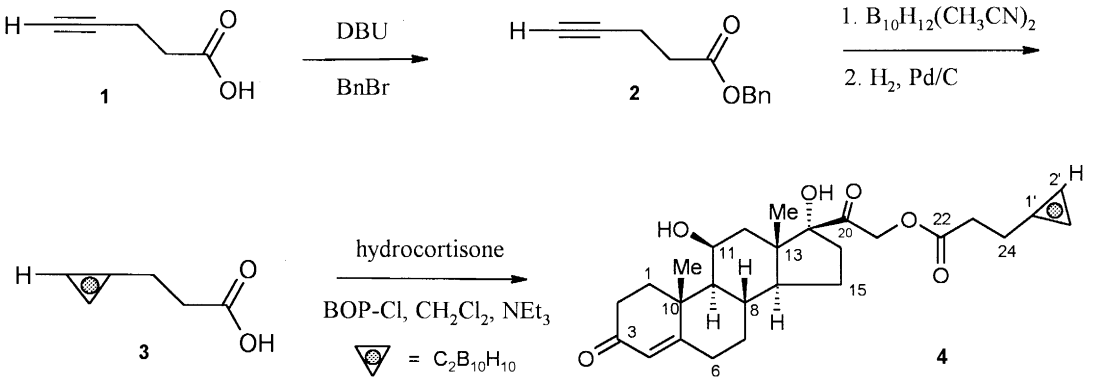
BNCS is to develop boron compounds that will concentrate selectively in arthritic cells as opposed to healthy ones following systemic administration.

Intra-articular administration of liposome entrapped cortisol palmitate has been shown to concentrate the steroid in arthritic synovial cells.[6] Our goal was to prepare a carborane analogue of the corticosteroid ester in hope that it would actively concentrate boron in the target cells. In order to prepare the desired carborane–steroid ester, we needed to develop an efficient coupling procedure between a carborane carboxylic acid and the hydroxyl group at C-21 of the corticosteroid.

The carboranyl acid **3** (Scheme 1) was chosen as a model compound for the development of the synthetic methodology. It was prepared by following Hawthorne's protocol,[7] which began by converting 4-pentynoic acid **1** to the benzyl ester **2**. The synthesis of **2** was best accomplished by reacting the acid with benzyl bromide in the presence of DBU. The ester **2** was converted to the carborane by heating it with $B_{10}H_{12}(CH_3CN)_2$ in acetonitrile to reflux for 72 h. The product, a colourless solid, was isolated by silica gel chromatography in reasonable yield (60%). The benzyl ester was converted to the acid **3** by hydrogenation (10 psi) in the presence of 10% palladium on carbon in excellent yield (98%).



Scheme 1.

Literature methods for the synthesis of carboranyl esters,[8] which include a carbodiimide-DMAP promoted coupling and the reaction of an alcohol with a carborane acid chloride derivative, failed to yield any of the desired steroid–carborane ester when applied to our system. Changes of reaction conditions (solvent, temperature, selection of base) did not improve the yield of product for either of the reported methods. An alternative approach was developed that entailed using a BOP-Cl (BOP-Cl=bis(2-oxo-3-oxazolidinyl)phosphinic chloride) promoted coupling reaction.[9] The acid **3**, in dichloromethane, was mixed with BOP-Cl and triethylamine prior to the addition of hydrocortisone. Under these conditions, the reaction afforded the hydrocortisone ester **4** in good yield (65%).[10] Under similar conditions, the 6α-methylprednisolone–carboranyl ester **5** (Fig. 1) was prepared in 66% yield.[11]

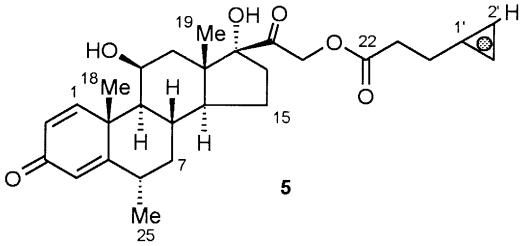


Fig. 1. 6α-Methylprednisolone–carboranyl ester **5**

IR spectra of compounds **4** and **5** exhibited strong B–H stretches at 2590 cm^{-1} and 2593 cm^{-1}, respectively. The proton and carbon-13 NMR spectra for **4** and **5** were assigned using 1-D and 2-D NMR techniques[10,11] and corroboration of the assignments was made by comparison with published NMR data for other corticosteroid esters.[12] The ^{11}B NMR for **4** and **5**, which consist of resonances ranging between −2.49 and −13.10 and −2.32 and −12.61 ppm, respectively, were consistent with the *closo*-carborane structures.

The proposed structure of **4** was confirmed through single crystal X-ray diffraction (Fig. 2). The carborane is a slightly distorted icosahedron in which the boron–boron and boron–carbon bond lengths range from 1.687(1) Å to 1.918(9) Å and 1.686(6) Å to 1.805(7) Å, respectively. The bond distance between C(24) and C(1′) is 1.530(7) Å which is similar to that for the corresponding carboranyl acid.

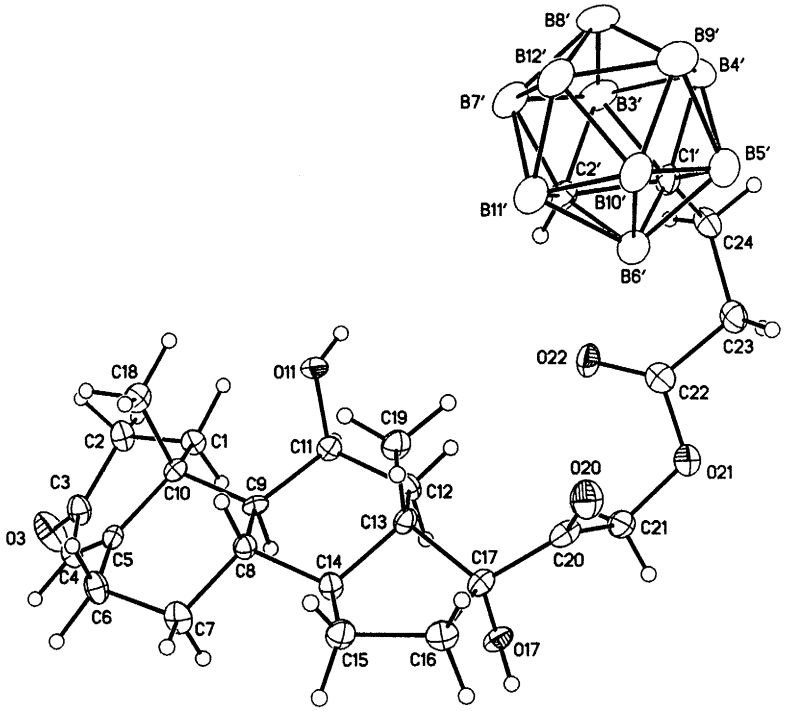


Fig. 2. ORTEP drawing of **4** (30% thermal ellipsoids) in which the hydrogen atoms attached to the boron atoms and a water molecule of crystallization have been omitted for clarity

The BOP-Cl coupling procedure is a new and efficient method for the synthesis of carboranyl esters under mild reaction conditions. We are currently utilizing this procedure to prepare a variety of different corticosteroid–carborane conjugates in concert with testing the efficacy of both free and encapsulated formulations of compounds **4** and **5**.

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10. The carborane **3** (591 mg, 2.73 mmol) was dissolved in dichloromethane (50 mL) and BOP-Cl (696 mg, 2.73 mmol) was added followed by freshly distilled triethylamine (553 mg, 5.47 mmol) and hydrocortisone (1.0 g, 2.76 mmol). The reaction was stirred at room temperature under nitrogen for 24 h whereupon additional BOP-Cl (348 mg, 1.37 mmol) and triethylamine (178 mg, 1.36 mmol) were added. The reaction was stirred for an additional 48 h whereupon it was diluted with dichloromethane (60 mL) and extracted with distilled water (50 mL), 0.1 M HCl (2×50 mL) and 10% $NaHCO_3$ (2×50 mL). The aqueous layers were combined and further extracted with dichloromethane (2×30 mL). The organic layers were combined and dried over sodium sulfate, filtered, and the solvent evaporated on a rotary evaporator. The resulting yellow solid was dissolved in a minimum volume of 10% hexanes in dichloromethane and the product (998 mg, 65%) isolated by silica gel chromatography (CH_2Cl_2). The product showed: TLC (5% CH_3OH in CH_2Cl_2) R_f=0.31; MS-NH_3CI: cluster of peaks centered around 562 (M+1); IR (nujol, cm^{-1}): 3479 (bw, OH), 2923, 2855 (s, CH), 2590 (s, BH), 1721 (s, ester CO), 1655 (s, ketone CO); ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.65 (d, $J_{4,6}$=1.37 Hz, H-4), 5.14 (AB, J=−17.48 Hz, H-21A), 4.89 (AB, H-21B), 4.43 (m, H-11), 3.99 (bs, H-2′), 2.65 (m, overlap, H-23, 24, 16β), 2.48 (m, H-6), 2.44 (m, H-2β), 2.32 (m, H-2α), 2.24 (m, H-6α), 2.19 (m, H-1β), 2.10 (m, H-12β), 2.04 (m, H-8), 2.02 (m, H-7β), 1.84 (m, H-1α), 1.77 (m, overlap, H-14, 15α), 1.71 (m, H-12α), 1.52 (m, H-16α), 1.45 (s, H-18), 1.39 (m, H-15β), 1.11 (m, H-7α), 1.00 (m, H-9α), 0.89 (s, H-19); ^{13}C NMR (126 MHz, $CDCl_3$): δ 205.06 (C-20), 199.26 (C-3), 172.39 (C-5), 170.54 (C-22), 121.83 (C-4), 89.04 (C-17), 73.81 (C-1′), 68.43 (C-21), 67.60 (C-11), 61.34 (C-2′), 55.79 (C-9), 51.71 (C-14), 47.13 (C-13), 39.42 (C-12), 39.00 (C-10), 34.60 (C-1), 33.84 (C-16), 33.57 (C-2), 32.90 (C-23 or 24), 32.60 (C-7), 32.33 (C-23 or C-24), 31.84 (C-6), 31.16 (C-8), 23.37 (C-15), 20.71 (C-18), 16.66 (C-19); ^{11}B NMR (160 MHz, $CDCl_3$): δ −2.52 (d), −5.87 (broad), −9.76 (d), −12.04, −13.10 (broad, overlap).
11. To a flask containing dichloromethane (25 mL) was added **3** (172 mg, 0.793 mmol), BOP-Cl (354 mg, 1.39 mmol), and triethylamine (276 μL, 2.31 mmol). These reagents were mixed whereupon α-methylprednisolone (349 mg, 0.80 mmol) was added. The heterogeneous reaction was stirred for 48 h under nitrogen and protected from light. The reaction was extracted with 0.1 M HCl (2×25 mL) and 10% $NaHCO_3$ (2×25 mL). The aqueous phases were combined and extracted with dichloromethane (2×20 mL). The organic fractions were combined and dried over sodium sulfate, gravity filtered and the solvent evaporated. Compound **5** was isolated by radial chromatography (100% EtOAc) followed by recrystallization from acetone (300 mg, 66%). The product showed: TLC (100% EtOAc): R_f=0.58; IR (NaCl, cm^{-1}): 3414 (b, OH), 2965, 2912 (s, CH), 2593 (s, BH), 1727 (ester CO), 1656 (ketone CO); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.24 (s, H-1), 6.25 (d, $J_{1,2}$=9.8 Hz, H-2), 6.00 (s, H-4), 5.01 (AB, J=−17.5 Hz, H-21A), 4.92 (AB, H-21B), 4.47 (m, H-11), 3.73 (bs, H-2′), 2.73 (m, H-16β), 2.64 (m, overlap, H-6, H-23, H-24), 2.20 (m, H-8), 2.07 (m, H-7β), 2.05 (m, H-12β), 1.80 (m, H-15α), 1.66 (m, H-12α), 1.60 (m, H-14), 1.46 (m, overlap, H-15β, H-16α), 1.43 (s, H-18), 1.10 (d, $J_{6,27}$=5.50 Hz, H-25), 1.01 (m, H-9), 0.93 (s, H-19), 0.79 (m, H-7α); ^{13}C NMR (126 MHz, $CDCl_3$): δ 204.25 (C-20), 186.69 (C-3), 173.15 (C-5 or C-22), 171.07 (C-5 or C-22), 156.72 (C-1), 127.53 (C-2), 119.77 (C-4), 89.66 (C-17), 73.76 (C-1′), 70.11 (C-11), 68.44 (C-21), 61.37 (C-2′), 55.86 (C-9), 51.36 (C-14), 47.92 (C-13), 44.24 (C-10), 42.92 (C-7), 39.73 (C-12), 34.88 (C-16), 33.11, 33.02, 32.65 (C-6, 23, 24) 31.10 (C-8), 23.77 (C-15), 21.53 (C-18), 17.73 (C-25), 16.98 (C-19); ^{11}B NMR (160 MHz, $CDCl_3$): δ −2.32 (d), −5.47 (d), −9.31 (d), −11.27, −12.61 (broad, overlap).
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