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Synthesis and characterization of 2-substituted bornane pharmacophores for novel cannabinergic ligands

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ABSTRACT

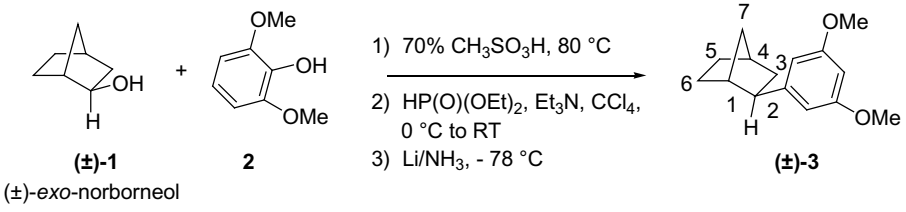
Analogously to the fenchyl and adamantyl groups, the bornyl and epimeric isobornyl groups are compact lipophilic substituents that can be incorporated into drug design to improve pharmacological or physicochemical properties. Methods are reported for the synthesis and characterization of 2-substituted norbornanes and bornanes that can serve as novel cannabinergic ligand intermediates.

1. Introduction

The pharmacological and physicochemical properties of certain drug classes can be modified by incorporating compact lipophilic moieties such as the fenchyl,[1,2] adamantyl,[3–7] and bornyl[8] groups. Examples include the CB2 inverse agonist SR144528[9] as well as the CB1 selective agonist AM411,[10] a crystalline classical cannabinoid analog with distinct pharmacological profiles.[11–14] Analogously, we have explored the incorporation of bornyl as well as the epimeric isobornyl groups into our cannabinergic drug design to further optimize ligand pharmacophoric properties. Here, we report our methods for the synthesis and characterization of 2-substituted norbornanes and bornanes that were prepared and characterized as intermediates in the synthesis of novel cannabinoid analogs.

2. Results and discussion

The *exo*-2-aryl analog **3** of norbornane was conveniently prepared (Scheme 1) by the same method that we described for the preparation of 1-adamantyl analogs.[10] Introduction of the norbornyl group by Friedel–Crafts type alkylation of 2,6-dimethoxyphenol (**2**) with (±)-*exo*-norborneol (**1**) in 70% methanesulfonic acid gave the racemic *exo*-analog (±)-**3** in three steps. However, the



(±)-1 (±)-*exo*-norborneol — 2 — (±)-3

Scheme 1. Synthesis of 2-norbornane (*exo*) analog via Friedel–Crafts type alkylation.

Abbreviations: AM411, 3-(adamant-1-yl)-6,6,9-trimethyl-6a,7,10,10a-tetrahydro-6*H*-benzo[*c*]chromen-1-ol; COSY, correlation spectroscopy; NMR, nuclear magnetic resonance; NOESY, nuclear Overhauser enhancement spectroscopy; SR144528, 5-(4-chloro-3-methylphenyl)-1-(4-methylbenzyl)-*N*-[(1*S*-*endo*)-1,3,3-trimethylbicyclo[2.2.1]hept-2-yl]-1*H*-pyrazole-3-carboxamide.

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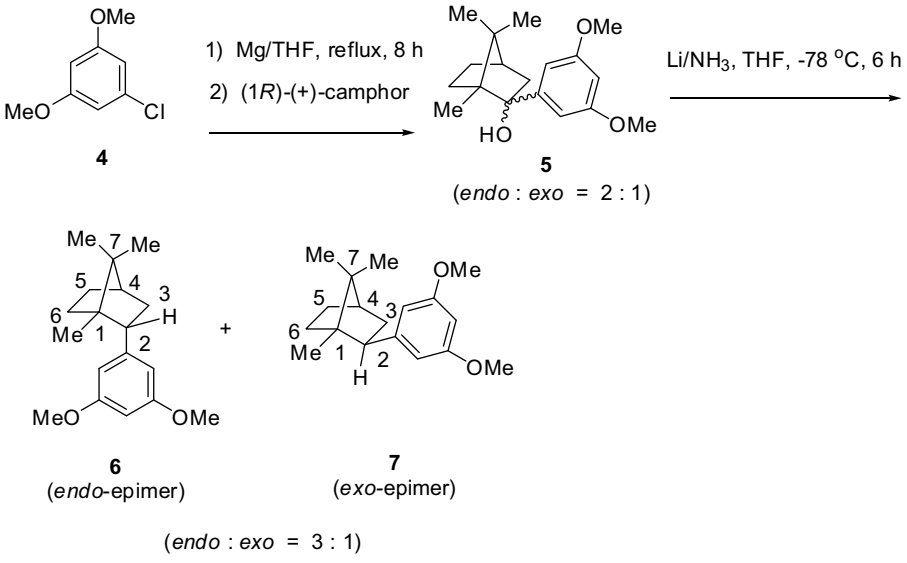
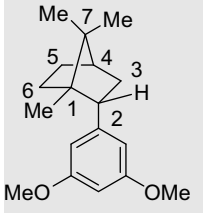


Scheme 2. Synthesis of 2-bornyl (*endo*) and 2-isobornyl (*exo*) epimers via a Grignard addition.

Wagner–Meerwein rearrangement racemizes optically active norbornanes and bornanes under acidic conditions and greatly limits the usefulness of this method. Thus, we chose a different approach for the synthesis of optically pure 1,7,7-trimethyl (bornane) derivatives that could also provide us with both *exo*- and *endo*-epimers.

Bornanes were selected for the further exploration of the key cannabinoid side chain pharmacophore as they represented a subtle stereochemical variation of the adamantyl group, both are ten carbon substituents. We now detail a useful method for preparing *endo*- and *exo*-epimers of aryl as well as alkyl analogs of 2-bornane with good stereocontrol. This route (Scheme 2) utilized a Grignard reaction with (1*R*)-(+)-camphor to prepare both *endo*-(bornyl) and *exo*-(isobornyl) 2-(3,5-dimethoxyphenyl)-1,7,7-trimethylbicyclo-[2.2.1]heptane analogs, **6** and **7**, respectively, that were synthetic intermediates for a new series of classical cannabinoid analogs.[15] The Grignard reagent prepared from 1-chloro-3,5-dimethoxybenzene (**4**) reacted with (1*R*)-(+)-camphor to give a 2:1 mixture of 3,5-dimethoxyphenyl adducts **5** that was inseparable by both flash column chromatography and chiral HPLC, though we were able to achieve separation after the subsequent step. The reported Grignard reaction of a preformed complex of (1*R*)-(+)-camphor with cerium(III) chloride[16,17] that gives *endo*-adducts exclusively was not used as both *endo*- and *exo*-adducts were desired. The major product of Grignard addition was the *endo*-adduct as expected from the corresponding reactions of Grignard reagents prepared from bromobenzene,[18,19] *p*-bromoanisole,[20] and *o*-bromoanisole.[21] The hydroxyl groups of the mixture of isoborneol and borneol analogs **5** were removed according to the methods reported for the corresponding anisole analog.[21] Hydrogenolysis of the 2:1 mixture with palladium on carbon produced some bornyl-skeletal rearrangement byproduct in addition to the desired reduction products. However, lithium/ammonia reduction cleanly afforded a 3:1 mixture of 5-bornyl-1,3-dimethoxybenzene (**6**) to 5-isobornyl-1,3-dimethoxybenzene (**7**), the reduction converting some of the *exo*-adduct of **5** to both reduction products **6** and **7**. A small quantity of the mixture was separated by HPLC on a Chiralpak AD column to unambiguously identify the major product as the *endo*-epimer 5-bornyl-1,3-dimethoxybenzene (**6**) that has an *exo*-benzylic proton, and the minor product as the *exo*-epimer 5-isobornyl-1,3-dimethoxybenzene (**7**) that has an *endo*-benzylic proton. The chemical shift differences and coupling patterns of the benzylic protons of **6** and **7** were in agreement with reported values for bornyl and isobornyl analogs.[22] The H-2$_{exo}$ proton of **6** was downfield relative to the H-2$_{endo}$ of **7**. Also, we observed ^4J-coupling[23] of the H-2$_{exo}$ benzylic proton of 5-bornyl-1,3-dimethoxybenzene (**6**) that was confirmed by COSY spectroscopy to be coupling to the coplanar H-6$_{exo}$. In contrast, the H-2$_{endo}$ benzylic proton of *exo*-epimer **7** was a characteristic doublet of doublets. The expected 'W' couplings of H-3$_{exo}$ to H-5$_{exo}$ for **6** and **7** were also observed. Only couplings of adjacent *exo*-protons H-3$_{exo}$ and H-5$_{exo}$ were observed to bridgehead H-4 of the bornane derivatives. Observed scalar coupling constants (J) determined by first order analysis of individual proton signals for the *endo*- and *exo*-epimers are given in Table 1. All assignments were ultimately confirmed by 2D NOESY experiments (see Supplementary data). It was also found that 2-alkyl substituted analogs, prepared in an analogous manner,[15] also have similar chemical shift effects, especially on H-6$_{exo}$. Our NMR data should be useful in the assignment of spectra from other bicyclo[2.2.1]heptane derivatives.[24,25]

Table 1
Observed coupling constants for *endo*-(bornyl) and *exo*-(isobornyl) epimers **6** and **7**



	endo-Epimer (bornyl) **6** J (Hz)		*exo*-Epimer (isobornyl) **7** J (Hz)
$J_{2exo,3exo}$	11.5	$J_{2endo,3exo}$	8.0
$J_{2exo,3endo}$	5.4	$J_{2endo,3endo}$	9.2
$^4J_{2exo,6exo}$	2.5	$^4J_{2endo,6exo}$	0.0
$J_{3exo,3endo}$	13.2	$J_{3exo,3endo}$	12.5
$J_{3exo,4}$	4.5	$J_{3exo,4}$	4.4
$^4J_{3exo,5exo}$	3.5	$^4J_{3exo,5exo}$	2.6
$J_{4,5exo}$	4.5	$J_{4,5exo}$	4.4
$J_{5exo,5endo}$	12.5	$J_{5exo,5endo}$	12[a]
$J_{5exo,6exo}$	12.0	$J_{5exo,6exo}$	12[a]
$J_{5exo,6endo}$	4.1	$J_{5exo,6endo}$	2.7
$J_{5endo,6exo}$	4.6	$J_{5endo,6exo}$	4.4
$J_{5endo,6endo}$	9.4	$J_{5endo,6endo}$	9.4
$J_{6exo,6endo}$	13.1	$J_{6exo,6endo}$	12[a]

[a] Coupling constants determined within 0.5 Hz.

Acknowledgments

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Supplementary data

Supplementary data (experimental procedures and characterizations of all compounds. 700 MHz ^{1}H NMR, COSY, and NOESY spectra for *endo*-epimer **6** and *exo*-epimer **7** in $CDCl_3$ solutions) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.07.029.

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