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Tandem Wagner-Meerwein Rearrangement-Carbocation Trapping in the Formation of Chiral Heterocyclic Ring Systems.

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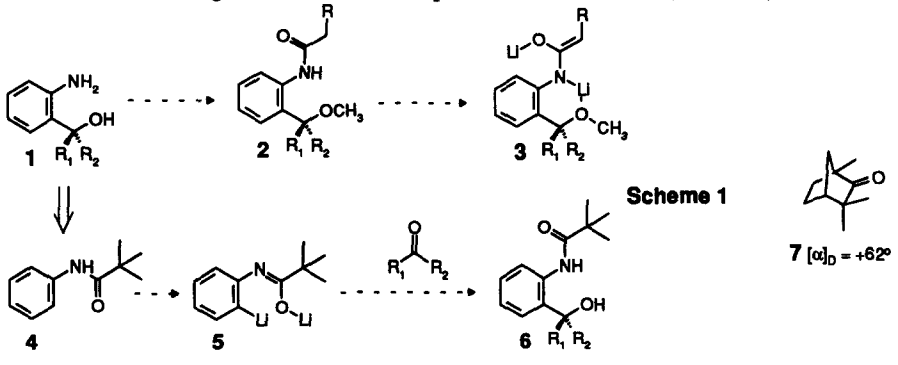
Abstract: Ortho lithiated protected anilines and phenols undergo exclusive addition to fenchone from the exo face. The corresponding adducts, under acidic conditions undergo cationic rearrangement followed by internal trapping of the new cation with amino, hydroxyl or methoxyl substituents to give enantiomerically pure chiral heterocyclic ring systems. The nature of the rearrangement is dependent on the donor group and its ability to stabilise a positive charge. With an amino donor group a product due to Wagner-Meerwein rearrangement is formed while with a methoxy donor group Nametkin rearrangement is the preferred pathway. © 1997 Elsevier Science Ltd.

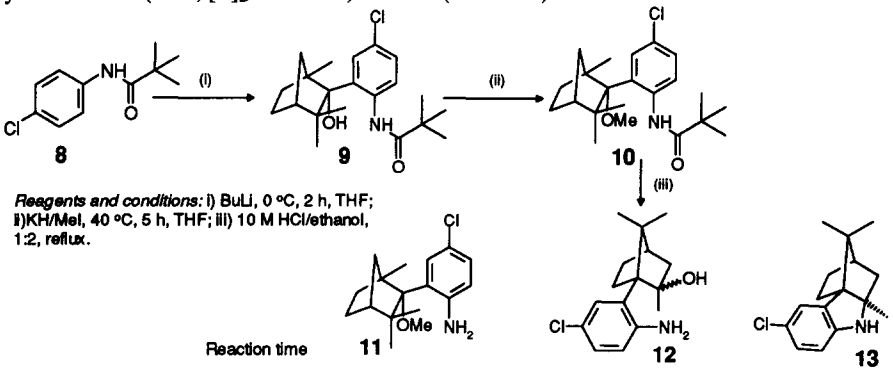
A common approach to the development of reagents for asymmetric synthesis is to utilise compounds derived from the chiral pool such as terpenes and amino acids. With the aim of developing synthetic methodology involving lithiated secondary amides we required substituted chiral *ortho*-hydroxymethylanilines **1** which could be coupled with carboxylic acid derivatives to provide the corresponding amides **2**. Dilithiation would then afford the chiral reagent **3** for use in nucleophilic addition reactions (Scheme 1).[1]



Scheme 1

The most obvious approach is to utilise directed ortho lithiation methodology on *N*-substituted anilines **4**[2] followed by addition of the aryllithium reagent **5** to a chiral ketone. Deprotection of the adduct **6** would afford the desired amino alcohol. In testing a range of chiral ketones for this purpose, we found that deprotection under acidic conditions is not compatible with the introduction of carbon skeleta that are susceptible to cationic rearrangement. However, with our work on the use of (+)-fenchone **7**, we find that these competing reactions have potential for other synthetic applications. This paper provides preliminary details of these studies.

Treatment of 4-chloropivanilide **8** with butyllithium (2 equiv.)[3] in THF for 2 h at 0 °C followed by exposure to (+)-fenchone **7** for 3 h at room temperature afforded the alcohol **9** (79%) as a single diastereomer resulting from exclusive exo attack.[4] Protection of the hydroxyl group proceeded smoothly with KH/excess MeI in THF at 40 °C for 5 h, to give the methyl ether **10** (70%). Competing amide methylation was not observed provided that the concentration of **9** was less than 0.1 M. The next step, removal of the pivaloyl group, proved to be difficult. Basic conditions were completely ineffective: refluxing in concentrated ethanolic KOH solution for several days only returned starting material. Triethyloxonium tetrafluoroborate in CH_2Cl_2 at 20 °C and $BF_3.OEt_2$ in EtOH under reflux also failed to induce any reaction indicating the hindered nature of the substrate. While acid hydrolysis with 1 M HCl/EtOH (1:2) under reflux had no effect, refluxing with 10 M HCl/EtOH (1:2) led to complete transformation of the starting material into three products. After 15 h the desired amino methyl ether **11** was obtained in 41% yield together with the amino alcohol **12** (32%, 65:35 mixture of diastereomers). Increasing the reaction time led to disappearance of **11** and **12** and after 24 h formation of a single diastereomer of the dihydroindole **13** (60%, $[\alpha]_D = -165.5°$) resulted (Scheme 2).

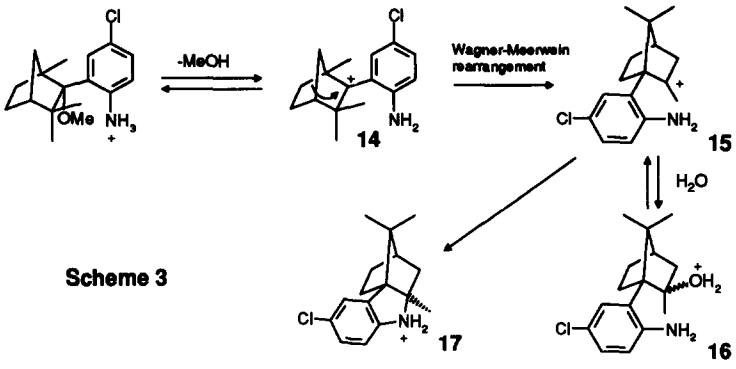


Scheme 2

Reaction time	11	12	13
15 h	41%	32%	0%
20 h	0%	37%	40%
24 h	0%	0%	60%

Under the strongly acidic conditions loss of methanol to give a benzylic carbocation **14** is followed by a Wagner-Meerwein rearrangement[5] to give **15** which is intercepted reversibly by water to give **16** (Scheme 3).[6] Irreversible intramolecular trapping by the amino group affords **17**.[7] A successful approach to a chiral aminoaryl fenchyl alcohol **18** (see Table) was finally achieved by using the trifluoroacetyl protecting group. Metallation of *ortho*-bromotrifluoroacetanilide[8] followed by treatment with (+)-fenchone gave the adduct in 72% yield. Deprotection of the amine was effected under basic conditions by refluxing in 3 M ethanolic NaOH for 24 h to give the product in 80% yield. Methylation (KH/MeI/THF) afforded the amino methyl ether in 86% yield. Compound **18** also underwent Wagner-Meerwein rearrangement upon acid hydrolysis (10 M HCl/EtOH, 1:2, reflux) to give **19** in 56% yield after 20 h (Table).[9]

In order to explore the scope of the tandem rearrangement-cation trapping reaction, we turned to the use of oxygen donors in the form of protected phenols. Ortho lithiation of the THP ether of phenol[10] followed by treatment of the aryllithium with (+)-fenchone gave **20** as a single diastereomer in 58% yield. Submission of **20** to acidic conditions (10 M HCl/EtOH, 1:2, reflux) resulted in complete transformation after 5 h to the dihydrobenzofurans **21** (23%) and **22** (57%) (Table).[9,11] The identity of **22** was revealed by 2D NMR analysis and its structure arises via an *exo*-3,2-methyl shift (Nametkin rearrangement)[5] followed by intramolecular trapping of the carbocation by the free hydroxyl group.

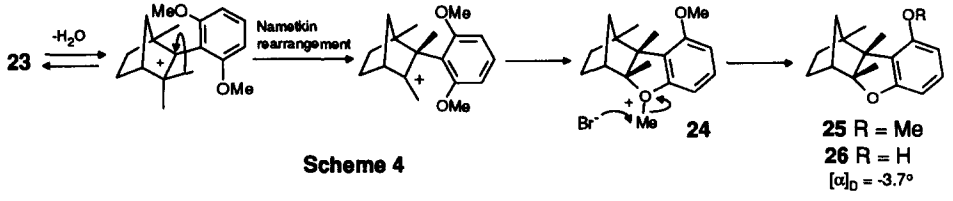


Scheme 3

starting material	yield (MM2 energy, $[\alpha]_D$)	yield (MM2 energy, $[\alpha]_D$)
18: Z = NH, R = H, R' = H	**19**: 56% (40.1 kcal/mol, -245.8°)	0% (31.5 kcal/mol)
20: Z = O, R = THP, R' = H	**21**: 23% (37.6 kcal/mol, N/D)	**22**: 57% (28.9 kcal/mol, -34.5°)
27: Z = O, R = CH_3, R' = H	**21**: 0%	**22**: 87%
23: Z = O, R = CH_3, R' = OCH_3	0%	**25**: 74% (-0.4°)

Table: Products arising from acid hydrolysis of fenchyl alcohol derivatives

In the context of using this reaction sequence to gain entry to biologically active cannabinoids and related compounds, lithiated 1,3-dimethoxybenzene[12] was examined next. Treatment of adduct **23** [formed in 68% yield from (+)-fenchone] with 48% HBr/acetic acid (1:4) under reflux led to rapid conversion (< 1 h) to the monomethyl ether **25**. Prolonging the reaction for 24 h then led to gradual cleavage of the second methyl ether to give **26** (42%) (Scheme 4). Both products arise from a tandem Nametkin rearrangement-carbocation trapping sequence: no products due to Wagner-Meerwein rearrangement were detected. The facility of the trapping in the last case suggests that trapping precedes demethylation which is assisted by the generation of an oxonium cation **24**. This was verified by treating the adducts from 1,3-dimethoxybenzene and anisole (**23** and **27** respectively) with 10 M HCl/EtOH (1:2) at room temperature, conditions that are too mild for normal demethylation to take place. Formation of the Nametkin products (**25** and **22** respectively) proceeded cleanly but more slowly (several hours) (Table).



Scheme 4

The tendency towards Wagner-Meerwein rearrangement-cation trapping verses Nametkin rearrangement-cation trapping appears to parallel the ability of the donor groups to stabilise a positive charge which in

turn must affect the reactivity of the intermediate benzylic carbocation.[13] Although the Nametkin rearrangement is a higher energy process, the resulting product which has a lower free energy than the corresponding Wagner-Meerwein product (see Table) is formed exclusively when the donor group is methoxyl suggesting that these reactions are under thermodynamic control. In contrast, the amino donor group is largely protonated under the acidic conditions and as such would destabilise a benzylic cation or disfavour its formation. In this case the energy barrier to the Wagner-Meerwein pathway is significantly higher and is the only pathway accessible. The intermediate case is that involving the THP ether **20**. Rapid hydrolysis to the free alcohol takes place and subsequent loss of water from the benzylic position leads to a mixture of the two rearrangement products paralleling the relative stabilising effect of the hydroxyl group.

In summary, we have shown that the treatment of (+)-fenchone with ortho lithiated protected anilines and phenols provides adducts which under acidic conditions generate carbocations that rearrange to give new enantiomerically pure five-membered heterocycles fused to a benzene ring and a terpenic carbocycle with high stereo- and regioselectivity. In principle, the manner in which the cationic rearrangement takes place and hence the nature of the new carbocation can be controlled by altering the nature of the ketone substrate. Approaches to six-membered heterocycles based on this sequence are currently being examined.

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9. All stereochemical assignments are based on the results of 1D and 2D NMR experiments. Selected ^{13}C NMR data (100 MHz, $CDCl_3$): **19** δ 20.5, 21.1, 23.6, 26.2, 27.3, 44.6, 46.4, 52.8, 63.9, 72.5, 109.7, 118.1, 123.4, 127.4, 128.3, 152.0; **21** δ 20.2, 20.5, 22.6, 24.3, 26.1, 32.0, 43.5, 45.9, 55.7, 110.0, 119.9, 123.4, 127.4, 129.6, 157.4; **22** δ 17.8, 19.5, 21.9, 23.6, 34.0, 42.2, 49.2, 50.8, 55.6, 97.3, 108.9, 119.6, 123.5, 128.0, 133.5, 158.7. Selected ^1H NMR data (400 MHz, $CDCl_3$, partial): **19** δ 0.94 (2×3H, s), 1.20 (3H, s), 2.46 (1H, ddd, J = 12.5, 3.2, 3.2 Hz); **21** δ 0.76 (3H, s), 0.90 (3H, s), 1.28 (3H, s), 2.65 (1H, ddd, J = 13.4, 3.1, 3.1 Hz); **22** δ 1.18 (3H, s), 1.23 (3H, s), 1.36 (3H, s), 2.22 (1H, dd, J = 4.4, 1.6 Hz).
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