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Total synthesis of the civet constituent (-)-2-((2R, 6R)-6-methyltetrahydro-2H-pyran-2-yl) acetic acid

Abstract

We describe the total synthesis of a glandular secretion of the Civet Cat, using tri-O-acetyl-D-glucan, a cheap and commercially available chiral building block.

Keywords: tetrahydropyran, civet cat compound, natural product, glandular secretion

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Introduction

Cis-6-methyltetrahydropyran-2-yl acetic acid , or civet, was isolated for the first time from the glandular secretions of the civet cat by Maurer and coworkersrs.[1] The THP-ring moiety of the structure of civet is also present in many natural products of biological and pharmacological significance.[2–9]Civet is used as an additive in the perfumery industry.[10] Due to its synthetically challenging cis-2,6-disubstituted tetrahydropyran moiety, several syntheses have been reported.[11–20] The structure of both enantiomers of civet is depicted in Figure 1. As part of our ongoing program focusing on the use of readily available chiral reagent tri-O-acetyl-D-glucal (3) for the synthesis of natural products,[21–28] we now wish to report the synthesis of (-)-Civet (2), using this reagent. Our retro synthetic basis is outlined in Figure 2.

Figure 1 Structures of (+)-Civet (**1**) and (-)-Civet (**2**).

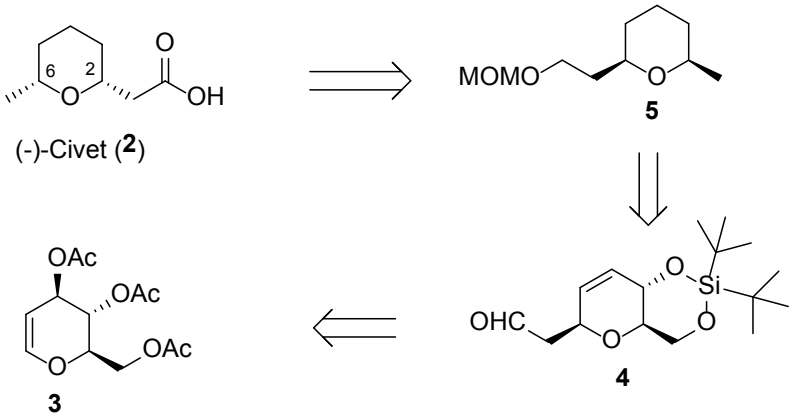


Figure 2 Retro synthetic scheme.

Results and discussion

We anticipated that compound**5** could be obtained from aldehyde 4, easily available from tri-O-acetyl-D-glucal (3) using a [3,3]-sigma tropic rearrangement we already developed for the synthesis of cis-2,6-disubstituted tetrahydropyrans.[29] Aldehyde 4 would then lead to 5, precursor of (-)-Civet (2). Accordingly we tried to prepare target compound 5 as outlined in Figure 3.

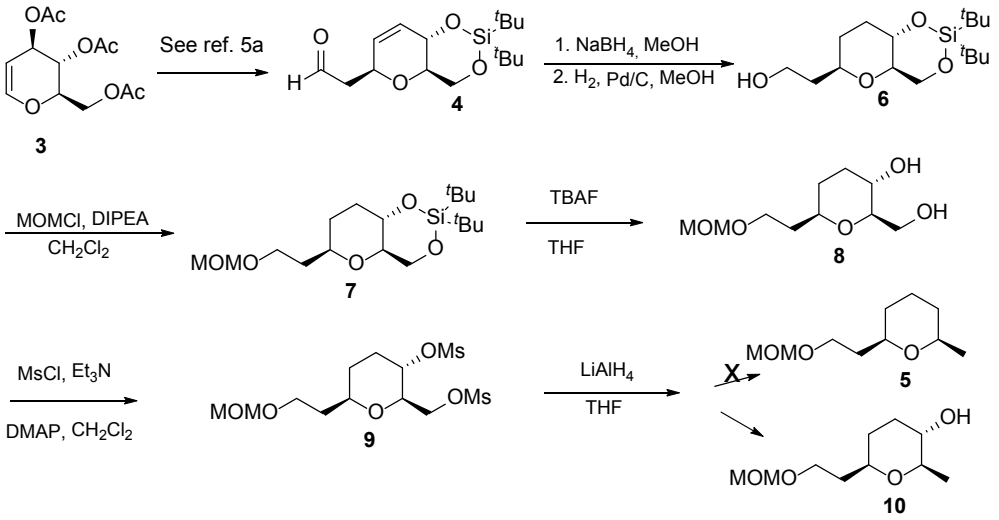
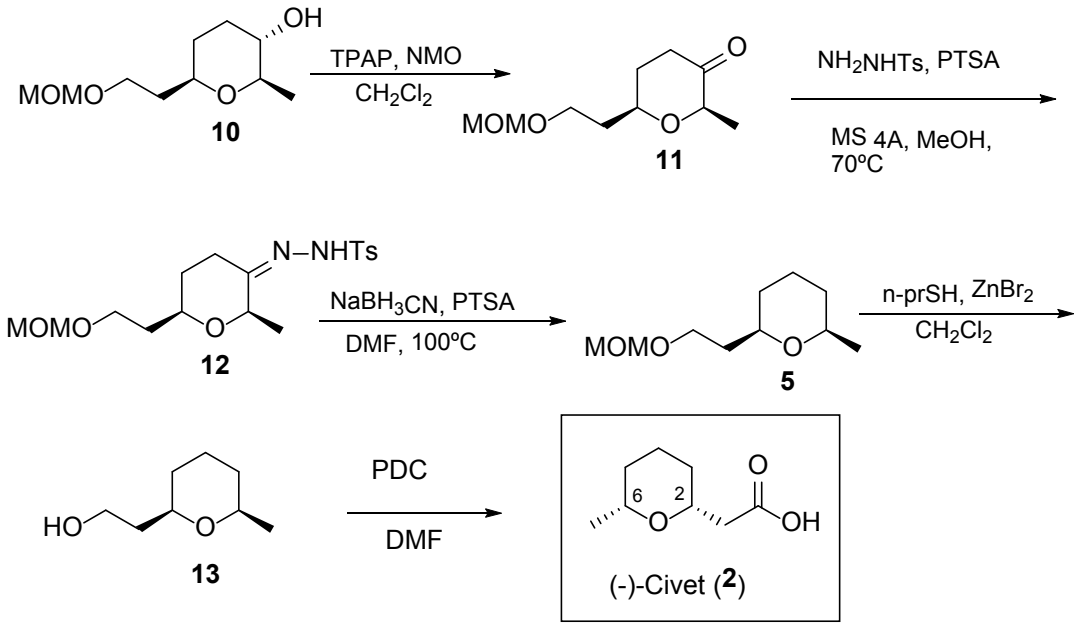


Figure 3 Unexpected synthesis of compound 10.

$NaBH_4$ reduction of aldehyde 4 followed by catalytic hydrogenation of the double bond afforded alcohol 6 in 90% yield (2 steps). MOM protection of the hydroxyl group of 6 gave 7which gave diol 8 upon reaction with TBAF in 80% yield (2 steps). Mesilation of diol 8 afforded 70% yield of dimesilate 9 which upon reaction with excess $LiALH_4$ at room temperature gave 94% yield of alcohol **10**, instead of target compound 5. To circumvent this unexpected result we decided to use the wolf-Kushner reaction[30] to prepare 5 from alcohol 10 as outlined in Scheme 3. TPAP oxidation of alcohol 10 afforded ketone 11 in 96% yields. Reaction of 11 with NH_2NHTs afforded 98% yield of hydrazone 12 which gave 62% yield of compound 5, upon reaction with $NaBH_3CN$. The stage was now set for the obtention of target compound 2 from 5. Accordingly the removal of the MOM protecting group[7] in 5 and PDC oxidation of the resulting alcohol 13 afforded title compound (-)-Civet (2) in 85% yield (2 steps).



Scheme 3 Synthesis of (-)-Civet (**2**).

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Conclusion

In conclusion, we have demonstrated that we could synthesize (2R, 6R)-(6-Methyltetrahydropyran-2-yl) acetic acid ((-)-Civet) using tri-O-acetyl-D-glucal as chiral building block. The use of this cheap and commercially available chiral compound for the synthesis of various natural products is now under way in our laboratories.

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Conflicts of interest

Author declares there is no conflict of interest.

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