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Improved and Flexible Synthetic Access to the Spiroindole Backbone of Cebranopadol

Daniel Wachtendorf, Marc Schmidtmann, and Jens Christoffers*

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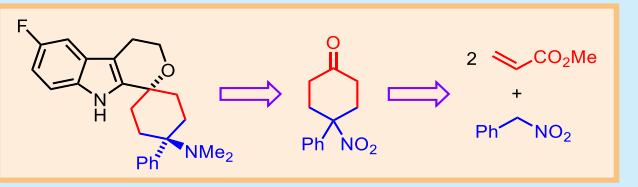
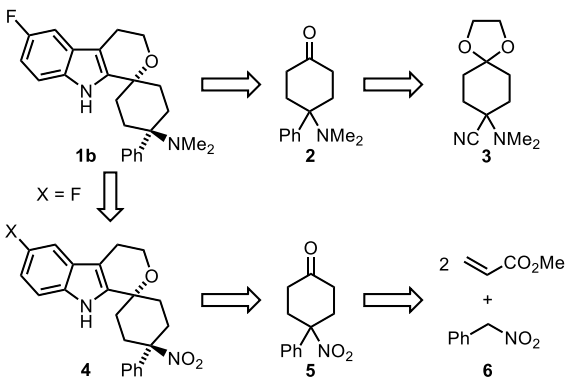
ABSTRACT: By changing the dimethylamino to a nitro group, a novel synthetic access to the spirocyclic opioid analgesic cebranopadol was developed that is much more efficient compared with the established route. On the basis of the α-acidity of α-nitrotoluene, the two-fold Michael addition to acrylate gave an acyclic precursor compound, which was easily transformed by Dieckmann condensation and decarboxylation to the cyclohexanone derivative needed for the annulation of the indole ring by an oxa-Pictet–Spengler reaction. As an additional benefit, the reduction of the nitro group furnished an amine, which could be late-stage-diversified to carboxamides, sulfonamides, ureas, and *N*-alkyl congeners. The transformation of the nitro group at the spirocyclic scaffold to the dimethylamino function of the actual title compound was achieved in one step with zinc/formic acid/formaldehyde in 83% yield.

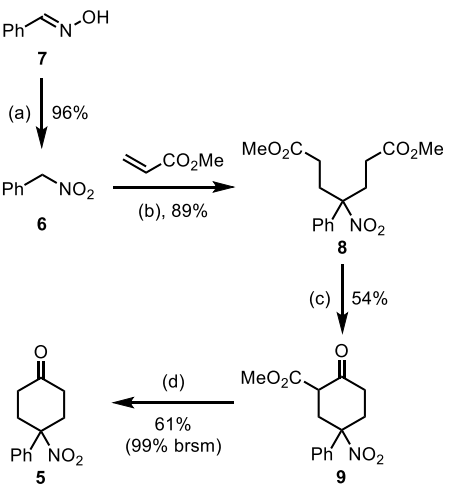


Cebranopadol (**1b**) is a novel opioid analgesic presently in clinical trials for the therapy of a variety of different acute and chronic pain states.[1] Its side-effect profile is superior to those of other typical opioids, and it is predominantly discussed for the treatment of pain related to cancer.[2] Cebranopadol (**1b**) was discovered in 2004 by chemists from the German pharmaceutical company Grünenthal.[3] The backbone structure of compound **1b** is a spiro[cyclohexan-1,1′-pyrano[3,4-*b*]indole] (Scheme 1). Compound **1b** is achiral, and it is the diastereoisomer with the 1,4-disubstituted cyclohexane ring in the relative trans configuration. The established synthesis of cebranopadol (**1b**) utilizes an oxa-Pictet–Spengler reaction of a 3-(hydroxyethyl)indole with cyclohexanone derivative **2** as a key step, which is accessed from acetal-protected α-aminonitrile **3**.[4] Therefore, the

Scheme 1. Established Synthetic Route to Cebranopadol (1b) from Aminonitrile 3 as Developed by Grünenthal and New Strategy via Nitro Compounds 4–6 (This Work)



Scheme 2. Preparation of Nitroketone 5[a]



[a]Reagents and conditions: (a) 5.0 equiv of H_2O_2 (30% in H_2O), 3.0 equiv of $(F_3CCO)_2O$, 0.5 equiv of urea, 4.0 equiv of $Na_2HPO_4{\cdot}2H_2O$, MTBE, 50 °C, 16 h. (b) 2.5 equiv of methyl acrylate, 0.5 equiv of DBU, CH_2Cl_2, 40 °C, 16 h. (c) 1.7 equiv of NaH, 0.1 equiv of MeOH, THF, 50 °C, 1 h. (d) 3.0 equiv of LiBr, 2.0 equiv of CSA, DMPU, 100 °C, 16 h.

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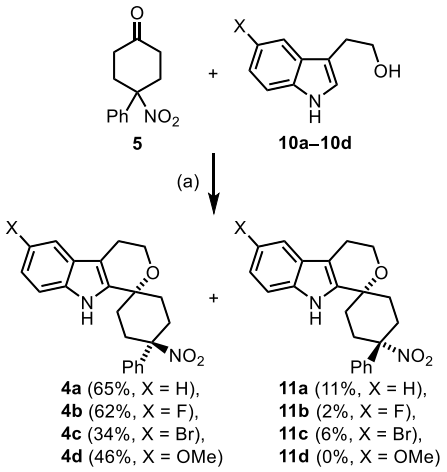
Scheme 3. Spirocyclization by oxa-Pictet–Spengler Reaction Furnishing Separable trans Isomers 4a–d and cis Isomers 11a–c[a]



[a]Reagents and conditions: (a) (1) 1.2 equiv of TFA, CH_2Cl_2, 50 °C, 16 h. (2) + NaOH (1 mol/L in H_2O), 0 °C, 0.5 h.

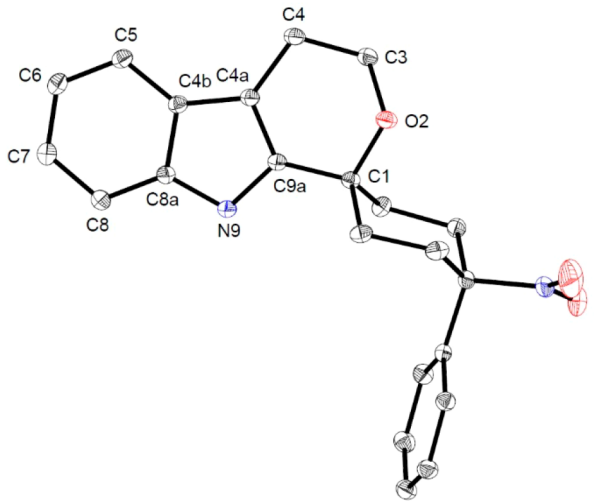
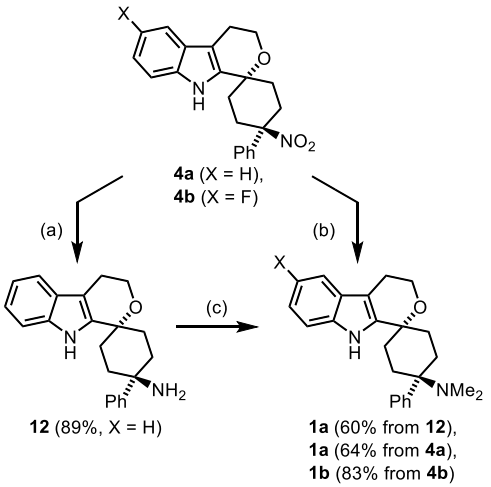


Figure 1. ORTEP representation of the structure of compound *cis*-**11a** in the solid state (as the solvate with DMSO-d_6). Ellipsoids are at the 50% probability level. Hydrogen atoms and DMSO-d_6 are omitted for clarity.

dimethylamino function was already installed in a very early stage of the overall sequence by the conversion of monoprotected 1,4-cyclohexanedione with $HNMe_2$/HCN to furnish compound **3** (67–99% yield).[4a] This intermediate was then converted with a phenyl Grignard reagent (28–99% yield) and deprotected to give ketone **2** (66–99% yield).[4a] The spirocyclization yielded 84% of trans diastereoisomer **1b**.[4b]

Herein we disclose an alternative approach to cebranopadol (**1b**), which first generates the nitro-congener **4** by an oxa-Pictet–Spengler reaction of cyclohexanone derivative **5**. There are two significant advantages of this new strategy: (1) The nitro group can, of course, be transformed into the dimethylamino function of the actual target compound **1b**. As an additional benefit, other nitrogen functionalizations could be easily installed, for example, *N*-alkyl or *N*-acyl derivatives, and thus a late-stage diversification of the spirocyclic scaffold is now feasible. (2) Second, the nitro-

Scheme 4. Reduction of the Nitro Group and Reductive Methylation[a]



[a]Reagents and conditions: (a) 40 equiv of Zn, 40 equiv of HCO_2H, MeOH, 50 °C, 16 h. (b) (1) As (a), (2) + 40 equiv of HCO_2H, 40 equiv of H_2CO (37% in H_2O), 70 °C, 16 h. (c) 8 equiv of HCO_2H, 3.3 equiv of H_2CO (37% in H_2O), MeOH, 70 °C, 16 h.

ketone **5** is readily accessed by the two-fold conjugated addition of α-nitrotoluene (**6**) to methyl acrylate followed by Dieckmann condensation and ester saponification/decarboxylation. This is much more convenient and less complicated than the synthesis of amino-ketone **2**.

The synthesis started with the preparation of α-nitrotoluene (**6**) in 96% yield (Scheme 2), which was accomplished by the oxidation of oxime **7** following a modified literature procedure.[5] The next two steps followed literature protocols recently reported for the analogous conversion of nitroethane.[6] The two-fold conjugated addition to methyl acrylate was DBU-catalyzed and gave the pimelic acid ester **8** in 89% yield, which was submitted to Dieckmann condensation with a stoichiometric amount of NaH in THF,[7] furnishing the β-oxoester **9** (54%) exclusively as the enol tautomer. The addition of some MeOH led to the formation of NaOMe and facilitated the reaction. The next step, the ester saponification with subsequent decarboxylation, required tedious optimization. After unsatisfying experimentation with several alternative procedures (see the Supporting Information for details), we finally succeeded with a modified Krapcho protocol in DMPU which followed some literature precedence.[8] The yield (61%) was moderate, but the starting material could be recovered (i.e., 99% based on recovered starting material (brsm)).

The 3-(2-hydroxyethyl)indole derivatives **10a–d** were accessed according to a literature report by Fischer indolization from the respective phenylhydrazine derivatives and dihydrofurane (as a precursor to 4-hydroxybutanal).[9] The oxa-Pictet–Spengler reaction proceeded straightforwardly when converting stoichiometric amounts of the nitroketone **5** with the indole derivatives **10a–d** in TFA–CH_2Cl_2 (Scheme 3).[10] In general, the trans diastereoisomers **4a–d** were hardly soluble and precipitated from the reaction mixture and were collected by filtration. The supernatants contained the cis diastereoisomers **11a–c** together with residual amounts of the trans isomers **4a–d**, which were separated and purified by chromatography. In the case of the methoxy-substituted compound, the cis isomer **11d** was not formed. The relative configuration of one representative was established by the

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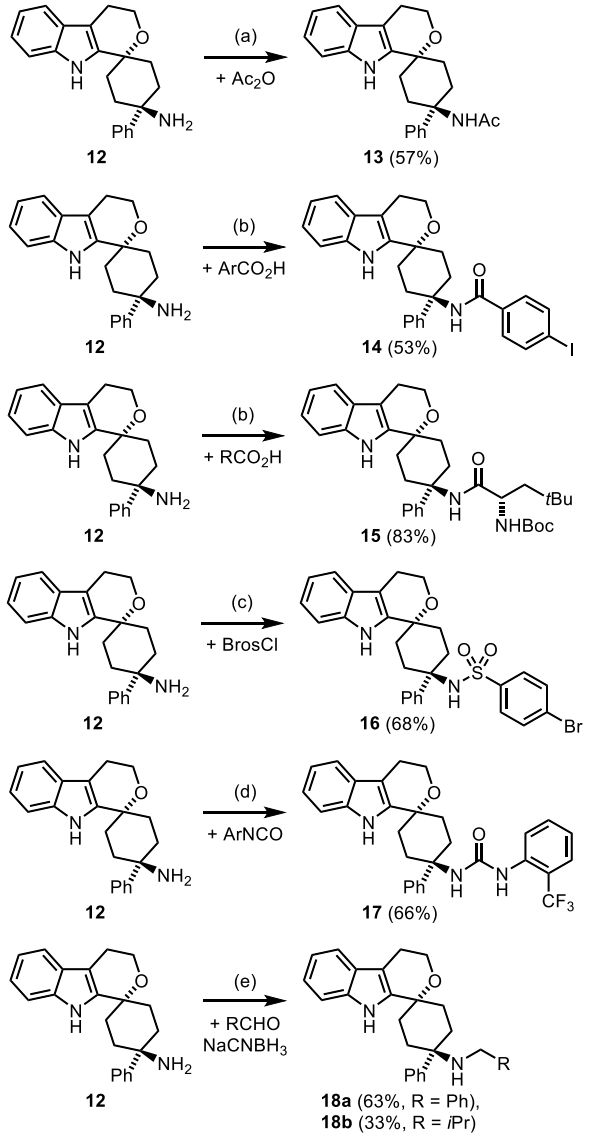
Scheme 5. Further Derivatization of the Primary Amino Function of trans Isomer 12[a]



[a]Reagents and conditions: (a) 1.2 equiv of Ac_2O, THF, 23 °C, 16 h. (b) 2 equiv of $ArCO_2H$ (for **14**, Ar = 4-IC_6H_4) or 2 equiv of RCO_2H (for **15**, RCO_2H = *N*-Boc-L-NpgOH), 2 equiv of EDC·HCl, 3 equiv of NEt_3, THF, 23 °C, 16 h. (c) 2 equiv of BrosCl (Bros = 4-$BrC_6H_4SO_2$), 2 equiv of NEt_3, THF, 23 °C, 16 h. (d) 2 equiv of ArNCO (Ar = 2-$CF_3C_6H_4$), THF, 75 °C, 16 h. (e) 1.1 equiv of RCHO, 0.5 equiv of $ZnCl_2$, 1.1 equiv of $NaCNBH_3$, THF, 23 °C, 16 h.

single-crystal X-ray structure analysis of the cis isomer **11a** (X = H, Figure 1; see the Supporting Information for details).

The trans isomer **4a** was subsequently submitted to the reduction of the nitro group with zinc to furnish the primary amine **12** (89%) (Scheme 4). The Brönsted acid formic acid was chosen because it was also used in the next step, the reductive amination with formaldehyde according to an Eschweiler–Clarke protocol,[11] which gave the respective dimethylamino derivative **1a** (60% from **12**). Consequently, the two reductions were then performed sequentially in one flask, and, indeed, the yield was superior to that for the two-step procedure via compound **12** (product **1a**, 64% from **4a**). Therefore, we only used the two-step–one-flask protocol for the preparation of cebranopadol **1b** from nitro compound **4b**. The 83% yield fully satisfied our expectations.

As introductorily proposed, one advantage of our new route is the late-stage derivatization of the spirocyclic scaffold. Therefore, standard transformations of the primary amino group, which are often found in the field of medicinal chemistry, were exemplarily performed for compound **12** (Scheme 5): carbox- and sulfonamide formation, preparation of ureas from isocyanates, and alkylation reactions by the reductive amination of aldehydes. First, acetamide **13** was formed in 57% yield by the treatment of amine **12** with Ac_2O. The amidation of compound **12** with an aromatic carboxylic acid utilized EDC as the coupling reagent (53% of product **14**). Coupling of the aliphatic carboxylic acid (*N*-Boc-L-neopentylglycine, *N*-Boc-L-NpgOH)[12] with EDC as the reagent gave amide **15** with a superior result (83% yield). Sulfonamide **16** was obtained in 68% yield from BrosCl and NEt_3. Conversion with an arylisocyanate in boiling THF gave urea **17** in 66% yield. Finally, reductive amination with benzaldehyde and isobutyraldehyde with $NaCNBH_3$ in an acidic environment[13] gave the secondary amines **18a** (R = Ph, 63%) and **18b** (R = *i*Pr, 33%).

In summary, a novel route to the Active Pharmaceutical Ingredient (API) cebranopadol **1b** was introduced. The key strategy was the use of a nitro function as a precursor for the dimethylamino group. The reduction/reductive amination of the nitro function is achieved with zinc/formic acid/formaldehyde in one step, furnishing the title compound **1b** in 83% yield. The nitro group furthermore allows for a straightforward approach to ketone **5** by Dieckmann condensation of the acyclic diester **8**, which is accessed by a two-fold Michael addition of α-nitrotoluene **6** to methyl acrylate. Compared with the preparation of the ketone **2** with the dimethylamino group present, our new approach is comparably efficient. However, the main advantage is that the nitro group at the spirocyclic scaffold allows for late-stage functionalization after the reduction to the primary amino group, as was shown exemplarily with the formation of carboxamides **13**–**15**, a sulfonamide **16**, a urea **17**, and the alkylated congeners **18** by reductive alkylations with aldehydes.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02234.

Synthesis, analytical data, and NMR spectra (PDF)

Accession Codes

CCDC 2012244 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Author

Jens Christoffers – *Institut für Chemie, Universität Oldenburg, D-26111 Oldenburg, Germany;* orcid.org/0000-0003-1433-6579; Email: jens.christoffers@uol.de; Fax: +49 441 798 3873

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Authors

Daniel Wachtendorf − *Institut für Chemie, Universität Oldenburg, D-26111 Oldenburg, Germany*
Marc Schmidtmann − *Institut für Chemie, Universität Oldenburg, D-26111 Oldenburg, Germany*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.0c02234

Notes

The authors declare no competing financial interest.

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