Pergamon

Tetrahedron Letters, Vol. 38, No. 1, pp. 159-162, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(96)02242-3

Synthesis of Enantiopure Aza-Analogues of Cocaine

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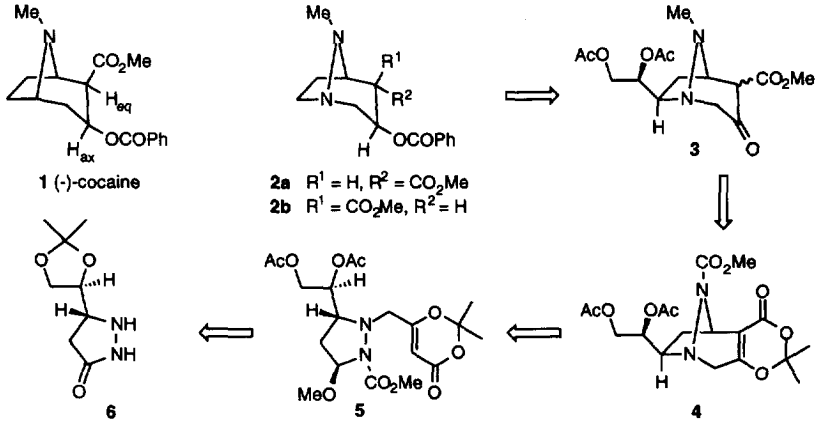
Abstract: An enantiopure aza-analogue of *pseudo*-cocaine was synthesized starting from a 5-substituted 3-pyrazolidinone by using an *N*-acylhydrazonium ion cyclization with a dioxenone nucleophile as the key step. Copyright © 1996 Elsevier Science Ltd

The tropane alkaloid (-)-cocaine (**1**) is well known for several remarkable physiological effects[1] and therefore has been subject of many studies over the last decades.[2] Because the mode of action of cocaine has not been completely elucidated yet, there is still an ongoing interest in novel cocaine analogues.[3] Most analogues obtained so far have been made starting from natural cocaine and hence are limited in terms of substitution pattern and type of framework atoms.[4] In this communication we wish to report a pathway to novel enantiopure aza-analogues of cocaine (*e.g.* **2**) that are obtained from simple starting materials. Our strategy is based on methodology that was recently developed for synthesizing enantiomerically pure bridged bicyclic hydrazines.[5,6]

Scheme 1

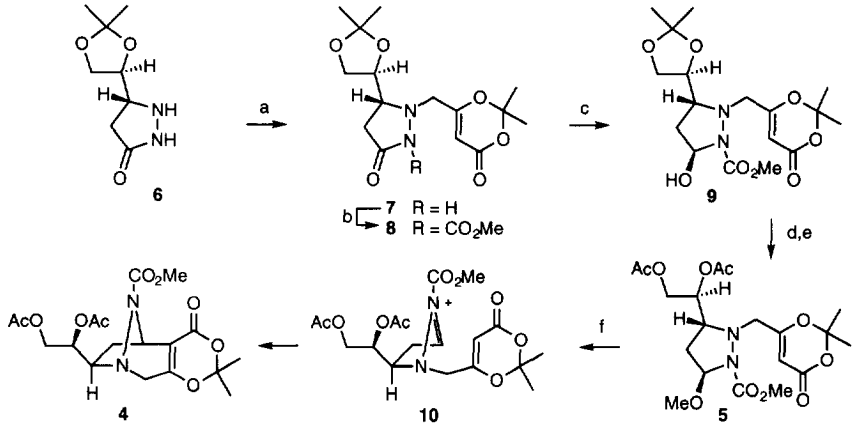


A retrosynthetic analysis is shown in Scheme 1, where the β-ketoester **3**, in analogy with several syntheses of cocaine derivatives,[2,3] serves as a suitable precursor to arrive at the desired substitution pattern, which also involves removal of the chiral auxiliary. The β-ketoester function is present throughout most of the synthesis in masked form as a dioxenone function[7] (*viz.* **4**) and liberated in a retro Diels-Alder reaction. Key

transformation in the whole sequence is the formation of **4** *via* stereoselective cyclization of the *N*-acylhydrazonium ion precursor **5**, which is prepared from the enantiomerically pure pyrazolidinone **6**.[5]

The synthesis of the tricyclic hydrazine **4** (which resembles the route described in the preceding paper)[5] is outlined in Scheme 2. It was decided to introduce the masked β-ketoester moiety at an early stage in the synthesis *via* deprotonation with sodium hydride (of the amide nitrogen N-2) and subsequent reaction with 6-(chloromethyl)-2,2-dimethyl-1,3-dioxen-4-one[8] to give the N-1 alkylated product **7** in 46% yield.[9] Attempts to increase the yield of the reaction by using other alkylation methods failed, which is probably partially due to the fact that the dioxenone function is thermally unstable. Methoxycarbonylation of N-2 with methyl cyanoformate to give **8**, followed by acid-catalyzed sodium borohydride reduction of the pyrazolidinone carbonyl afforded pyrazolidinol **9** as the *trans*-isomer in excellent yield.

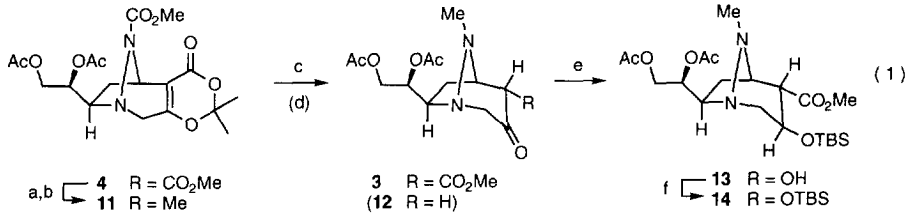
Scheme 2



Reagents and conditions: a) NaH (1 equiv), THF, rt, 30 min, then 6-(chloromethyl)-2,2-dimethyl-1,3-dioxen-4-one (1.2 equiv), 0 °C → rt, 4 h, 46%; b) NaH (1 equiv), THF, rt, 30 min, then $NCCO_2Me$ (3 equiv), 0 °C → rt, 4 h, 92%; c) $NaBH_4$ (4 equiv), EtOH, H_2SO_4 (cat), -25 °C, 4 h, 94%; d) HCl/MeOH, 0 °C, 1 h; e) Ac_2O (10 equiv), pyridine, DMAP (cat), rt, 18 h, 96% (2 steps); f) $BF_3{\cdot}OEt_2$ (4 equiv), CH_2Cl_2, -78 °C → rt, 18h, 98%.

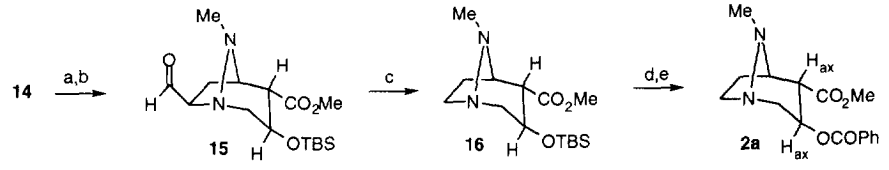
Conversion of **9** into the hydrazonium ion precursor **5** was achieved by acidic cleavage (HCl/MeOH) of the isopropylidene function with concomitant methanolysis of the pyrazolidinol, followed by acetylation of the resulting diol fragment. Treatment of **5** with $BF_3{\cdot}OEt_2$ resulted in the formation of the *N*-acylhydrazonium ion intermediate **10**, which cyclized to give the tricyclic hydrazine **4**[10] as a single diastereoisomer in virtually quantitative yield. With this key intermediate in hand, we decided to execute the required further transformations of the system in the order (a) conversion of the methyl carbamate into an *N*-methyl function, (b) thermal cleavage and subsequent reduction of the dioxenone moiety and (c) removal of the remaining auxiliary. Parts of these transformations are shown in eq 2, *i.e.* selective cleavage of the carbamate group with Me_3SiI afforded the corresponding free hydrazine, which was then methylated *via* a reductive amination process ($(H_2CO)_n$, $NaBH_3CN$, AcOH (cat)) to arrive at compound **11** in 81% yield. Then, demasking of the β-ketoester was achieved by heating the dioxenone **11** in the presence of an excess of MeOH in a sealed tube at 170 °C. A retro Diels-Alder reaction led to the corresponding acyl ketene, which was trapped with methanol to provide the methyl ester **3** in excellent yield. Formation of **3** is usually accompanied by traces of the decarboxylation product **12**, which could be obtained in good yield if water was used in this reaction instead of methanol. The latter product (a so-called aza-tropinone derivative) is an interesting precursor for preparing novel aza-analogues of tropinone and tropine systems, such as atropine.[11] Sodium borohydride reduction of the β-ketoester **3** at -15 °C in AcOH/THF (pH 6-7, according to wet pH-paper) afforded exclusively the desired

equatorial alcohol **13**,[12] which was protected as the stable *tert*-butyldimethylsilyl ether **14** in order to study the removal of the diol fragment.



Reagents and conditions: a) Me_3SiI (1.2 equiv), MeCN, 40 °C, 2h; b) 37% aq H_2CO (10 equiv), $NaBH_3CN$ (1.6 equiv), AcOH (cat), MeCN, rt, 4h, 81%; c) MeOH (15 equiv), xylene, sealed tube, 170 °C, 45 min, 94%; d) H_2O (15 equiv), xylene, sealed tube, 170 °C, 45 min, 78%; e) $NaBH_4$ (1.1 equiv), AcOH (pH 6/7), THF, -15 °C, 3h; f) TBSOTf (3 equiv), 2,6-lutidine (5 equiv), DMAP (cat), CH_2Cl_2, 0 °C → rt, 5h, 52% (2 steps).

Efficient removal of the diacetate moiety involved methanolysis of both acetate functions (K_2CO_3, MeOH) and periodate cleavage of the resulting diol to produce aldehyde **15**, followed by a reductive decarbonylation using Wilkinson's catalyst[13] to give **16** in 46% yield over three steps (eq 2). Smooth deprotection of the silyl ether with HF·pyridine and subsequent benzoylation afforded **2a**,[14] one of the target aza-analogues of cocaine. The stereochemistry (methyl ester equatorial, benzoate equatorial; referred to as '*pseudo*' in cocaine nomenclature)[1b] was confirmed by comparison of the coupling constant between H-3 (α to the benzoate; δ = 3.24 ppm) and H-4 (α to the methyl ester; δ = 5.50 ppm; $J_{3,4}$ = 10.4 Hz; characteristic for an axial-axial coupling) with the literature value for *pseudo*-cocaine ($J_{3,4}$ = 10.9 Hz).[15] Unfortunately, attempts to isomerize the ester function to give **2b** by using conditions described in cocaine literature (*e.g.* reflux in H_2O)[16] failed in this system.



Reagents and conditions: a) K_2CO_3 (2 equiv), MeOH, rt, 30 min; b) $NaIO_4$ (2 equiv), CH_2Cl_2/H_2O (10:1), rt, 45 min; c) $(PPh_3)_3RhCl$ (1 equiv), xylene, reflux, 3h, 46% (3 steps); d) HF·pyridine, CH_2Cl_2, 0 °C, 20 min; e) PhCOCl (5 equiv), CH_2Cl_2/pyridine (10:1), 0 °C → rt, 18h, 53% (2 steps).

In summary, we have shown that our methodology for preparing enantiopure bicyclic hydrazines[5] can be successfully applied to the synthesis of aza-derivatives of cocaine. Key features of the route include the use of a dioxenone function as a masked β-ketoester, stereoselective cyclization *via* an enantiopure *N*-acylhydrazonium intermediate and successful removal of the diol auxiliary. Sofar the most advanced compound, an aza-analogue of *pseudo*-cocaine could not be isomerized to 'aza-cocaine'. Studies are now in progress to arrive at the desired relationship between methyl ester and benzoate at an earlier stage of the synthesis. The results of these studies will be reported in a full account of this work.

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8. Boeckman, R.K.; Perni, R.B.; Macdonald, J.E.; Thomas, A.J. *Org. Synth.* **1987**, *66*, 194.
9. All new materials were obtained in pure form and appropriately characterized by spectroscopic methods (IR, ^{1}H NMR, ^{13}C NMR, high resolution mass spectral data and rotation values).
10. Data for **4**: colorless oil; $[\alpha]^{22}_D$ -6.0 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3000, 2955, 1745, 1735, 1725, 1640, 1420, 1375, 1280, 1230 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.15 (m, 1H, H-5), 4.94-4.90 (m, 1H, CHO), 4.33 (dd, *J* = 11.9, 4.0 Hz, 1H, C*H*HO), 4.08 (dd, *J* = 11.9, 5.9 Hz, 1H, CH*H*O), 4. 02 (d, *J* = 18.3 Hz, 1H, NC*H*H), 3.72 (s, 3H, CO_2Me), 3.42-3.37 (m, 1H, H-7), 3.22 (d, *J* = 18.3 Hz, 1H, NCH*H*), 2.36 (dd, *J* = 12.3, 7.8 Hz, 1H, H-6), 2.04 (s, 3H, Ac), 2.02 (s, 3H, Ac), 1.96-1.90 (m, 1H, H-6), 1.66 (s, 3H, Me), 1.64 (s, 3H, Me); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 170.0, 161.4, 158.4, 107.4, 106.4, 71.9, 67.0, 63.0, 58.8, 53.1, 51.2, 39.3, 26.8, 23.0, 20.9, 20.7; HRMS calculated for $C_{18}H_{24}N_2O_9$ 412.1482, found, 412.1502.
11. This method offers the possibilty to synthesize enantiopure analogues of the achiral tropinone and tropine systems.
12. This selectivity is completely opposite to what was observed in a similar reduction of 2-(carbomethoxy)tropinone where mainly the axial alcohol was formed.[15] However, sodium borohydride reduction of 6- and 7-substituted 2-(carbomethoxy)tropinones was recently reported to give only the equatorial alcohol[3d] indicating that the selectivity in the reduction of **3** is probably due to the presence of a substitent on the 5-membered ring.
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14. Data for **2b**: colorless oil; $[\alpha]^{22}_D$ + 22.5 (*c* 0.19, $CHCl_3$); IR ($CHCl_3$) ν_{max} 2955, 2924, 1742, 1717, 1277, 1113, 713 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97-7.95 (m, 2H, Ar-H), 7.55-7.51 (m, 1H, Ar-H), 7.43-7.39 (m, 2H, Ar-H), 5.50 (td, *J* = 10.4, 6.5 Hz, 1H, H-3), 3.68-3.67 (m, 1H, H-5), 3.65 (s, 3H, CO_2Me), 3.35 (dd, *J* = 13.1, 6.5 Hz, 1H, H-2), 3.39-3.31 (m, 1H, H-7), 3.24 (dd, *J* = 10.4, 3.0 Hz, 1H, H-4), 3.17-3.11 (m, 1H, H-7), 3.01 (dd, *J* = 13.1, 10.4 Hz, 1H, H-2), 2.40 (s, 3H, NMe), 2.20-2.05 (m, 2H, H-6); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 165.7, 133.1, 129.8, 129.6, 128.3, 65.3, 63.2, 58.6, 52.1, 51.5, 49.2, 40.8, 26.6; HRMS calculated for $C_{16}H_{20}N_2O_4$ 304.1423, found 304.1446.
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(*Received in UK* 5 *November* 1996; *accepted* 15 *November* 1996)