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A novel biomimetic condensation of 2-deoxyribose, aryl amine and acetyl acetone to bicyclic aminols catalyzed by $InCl_3$

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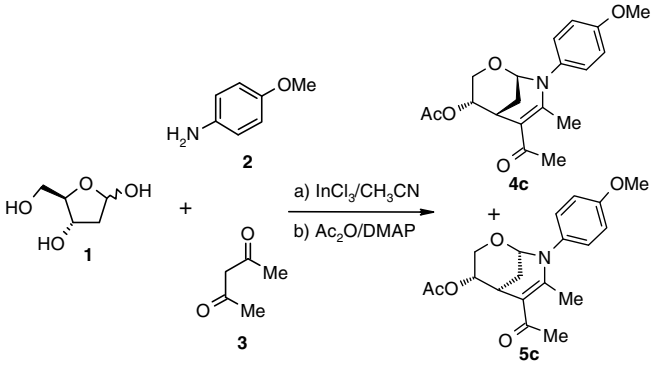
Abstract

2-Deoxyribose, an aryl amine and acetyl acetone undergo smooth cyclocondensation in the presence of 10 mol % of $InCl_3$ under mild conditions to afford the corresponding sugar-derived bicyclic aminols in good yields with moderate diastereoselectivity. This reaction is reminiscent of the celebrated tropinone synthesis of Robinson. The structures of the products are established by using various NMR experiments and X-ray crystallographic studies.

Keywords: 2-Deoxysugars; Indium trichloride; Aryl amines; Heterobicycles

Multi-component, one-pot syntheses have received considerable attention because of their wide range of applications in pharmaceutical chemistry for generation of structural diversity and combinatorial libraries for drug discovery.[1] The ready availability of a wide range of carbohydrates in Nature and their multi-chiral architecture, coupled with their well-defined stereochemistry, make them attractive starting materials in organic synthesis.[2,3] In particular, 2-deoxy-D-ribose is a valuable synthetic intermediate for various organic transformations.[4,5] Recently, indium trichloride has emerged as a mild and water-tolerant Lewis acid imparting high regio-, chemo- and diastereoselectivity in various organic transformations.[6] Compared to conventional Lewis acids, indium trichloride, in particular, has advantages of low catalyst loading and moisture stability.

In continuation of our interest in exploring the synthetic utility of indium(III) chloride,[7] we herein disclose a novel method for the synthesis of sugar-based, bicyclic aminols from 2-deoxyribose, an aryl amine and acetyl acetone. Initially, we attempted a three-component reaction of 2-deoxyribose, *p*-anisidine and acetyl acetone in the presence of 10 mol % of $InCl_3$. The reaction proceeded smoothly in acetonitrile at room temperature and the product was obtained in 91% yield as a mixture of **4c** and **5c** in a 1:1 ratio after acetylation (Scheme 1, Table 1).



Scheme 1. Preparation of **4c** and **5c**.

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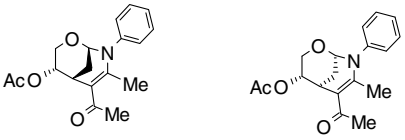
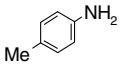
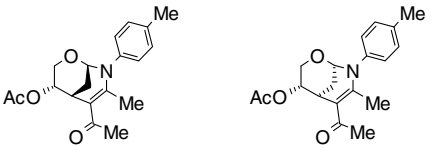
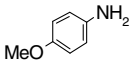
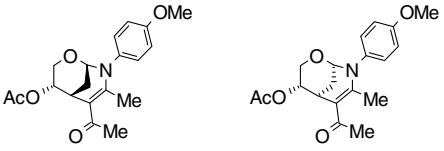
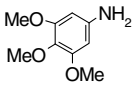
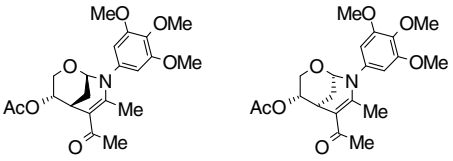
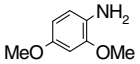
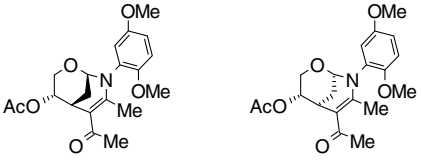
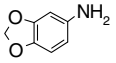
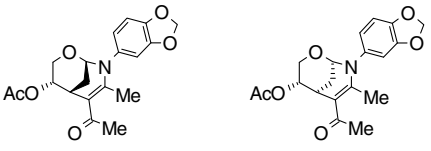
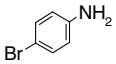
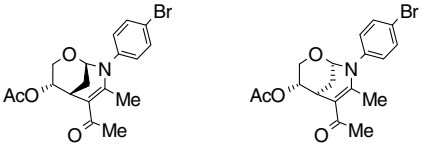
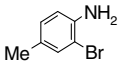
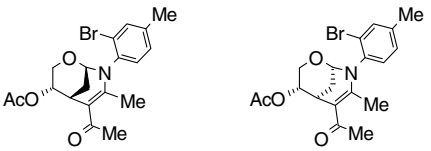
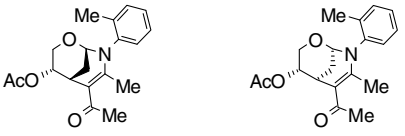
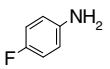
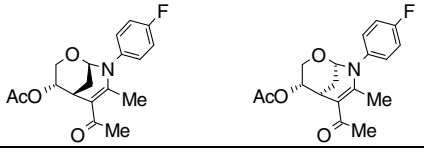
Table 1
$InCl_3$-catalyzed three-component coupling of 2-deoxy-ribose, acetyl acetone and aryl amines

Entry	Substrate	Aryl amine	Products[a]	Time (h)	Yield[b,c] (%)
a	2-Deoxy-D-ribose + acetyl acetone			5.0	93
b	2-Deoxy-D-ribose + acetyl acetone			5.5	85
c	2-Deoxy-D-ribose + acetyl acetone			5.0	91
d	2-Deoxy-D-ribose + acetyl acetone			6.0	83
e	2-Deoxy-D-ribose + acetyl acetone			5.5	80
f	2-Deoxy-D-ribose + acetyl acetone			4.5	85
g	2-Deoxy-D-ribose + acetyl acetone			6.0	82
h	2-Deoxy-D-ribose + acetyl acetone			5.0	87
i	2-Deoxy-D-ribose + acetyl acetone			5.5	75
j	2-Deoxy-D-ribose + acetyl acetone			6.5	73

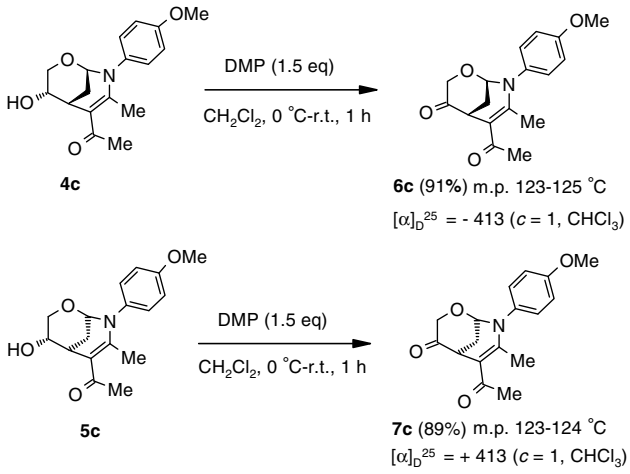
[a] All products were characterized by NMR, IR and mass spectroscopy.
[b] Yield refers to pure products after chromatography.
[c] Diastereomers were formed in 1:1 ratio.

These diastereoisomers, **4c** and **5c** could be easily separated by column chromatography and characterized by extensive NMR experiments. Compound **4c** was characterized thoroughly with the help of various NMR experiments including 2-D nuclear Overhauser effect spectroscopy (NOESY), heteronuclear single-quantum correlation spectroscopy (HSQC) and heteronuclear multiple bond correlation spectroscopy (HMBC). The NMR data suggest that the molecular structure of **4c** consists of a [1.3.3]bicyclononene-like structure. The bridgehead protons H3 and H5 and the methylene group in the bridge ($H4_{(pro\text{-}R)}$ and $H4_{(pro\text{-}S)}$) all showed small couplings ($J_{H2–H3} = 4.4$ Hz, $J_{H3–H4(pro\text{-}S)} = 4.6$ Hz, $J_{H4(pro\text{-}S)H3} = 2.2$ Hz, $J_{H3–H4(pro\text{-}R)} = 3.0$ Hz, and $J_{H4(pro\text{-}R)\text{-}H5} = 3.0$ Hz; Fig. 1). The two six-membered rings of the bicyclononene moiety differ in their conformations. The chair conformation of the oxygen-containing six-membered ring is supported by the NOESY cross peak $H2/H4_{(pro\text{-}S)}$ as well as the large diaxial coupling $J_{H1(pro\text{-}R)–H2} = 10.4$ Hz and other small couplings mentioned above. NOE correlations, $H5/H_{ortho}$ and $H1_{(pro\text{-}R)}/H_{ortho}$ further confirm that the N–Ph group is on the same side as the ring oxygen, while the location of the methyl group adjacent to the ring nitrogen was supported by the NOE correlation $H6/H_{ortho}$. Additionally, HMBC correlations, C11/H5, C1/H5, C1/H3, C7/H5, C8/H2 and $C8/H4_{(pro\text{-}R)}$ are in complete agreement with the proposed structure. The minimum energy structure supporting these conclusions is shown in Figure 1.[8]

Further, the structure of **4c** was established by chemical correlation. Thus, the oxidation of both **4c** and **5c** with Dess–Martin periodinane gave the corresponding ketones **6c** and **7c** which exhibit identical NMR spectra and mps but opposite optical rotation which confirms the structure of **4c** (Scheme 2).

The NMR data for **5c** supports a structure with opposite configuration at C3 and C5 compared to **4c**. However, due to the opposite configuration at C3 and C5 the six-membered chair flips and the acetyl group at C2 adopts an axial position. The bridgehead protons H3 and H5 and the methylene group in the bridge ($H4_{(pro\text{-}R)}$ and $H4_{(pro\text{-}S)}$) all show small couplings ($J_{H3–H4(pro\text{-}S)} = 3.1$ Hz, $J_{H4(pro\text{-}S)–H3} = 3.0$ Hz, $J_{H4(pro\text{-}R)–H5} = 2.2$ Hz, and $J_{H4(pro\text{-}R)–H5} = 3.8$ Hz). The NOE correlations, $H5/H_{ortho}$ and $H1_{(pro\text{-}S)}/H_{ortho}$ confirm that the N–Ph group is on the same side as the ring oxygen as in **4c**, while the location of the methyl group adjacent to the ring nitrogen was supported by the NOE correlation $H6/H_{ortho}$. Additionally, HMBC correlations, C11/H5, C1/H5, C1/H3, C7/H5, C8/H2 and $C8/H4_{(pro\text{-}S)}$ are in complete agreement with the proposed structure. The minimum energy structure supporting these conclusions is shown in Figure 2.[8]

The structure of **5c** was further confirmed by X-ray crystallographic studies (Fig. 3).[10]



Scheme 2. Oxidation of **4c** and **5c**.

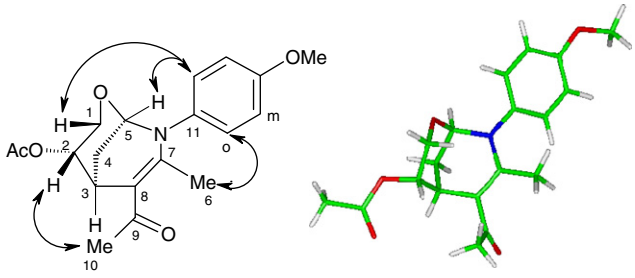


Fig. 2. Important NOEs and energy-minimized structure of **5c**.

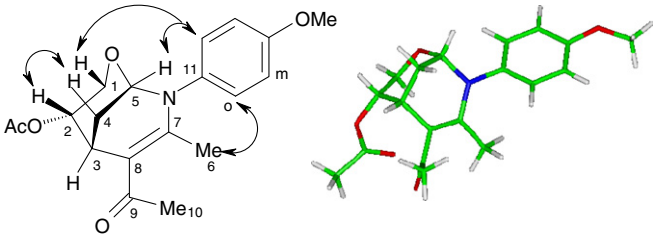


Fig. 1. Important NOEs and energy-minimized structure of **4c**.

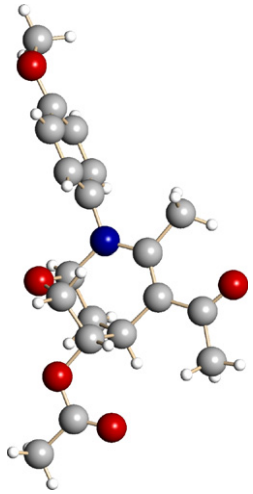
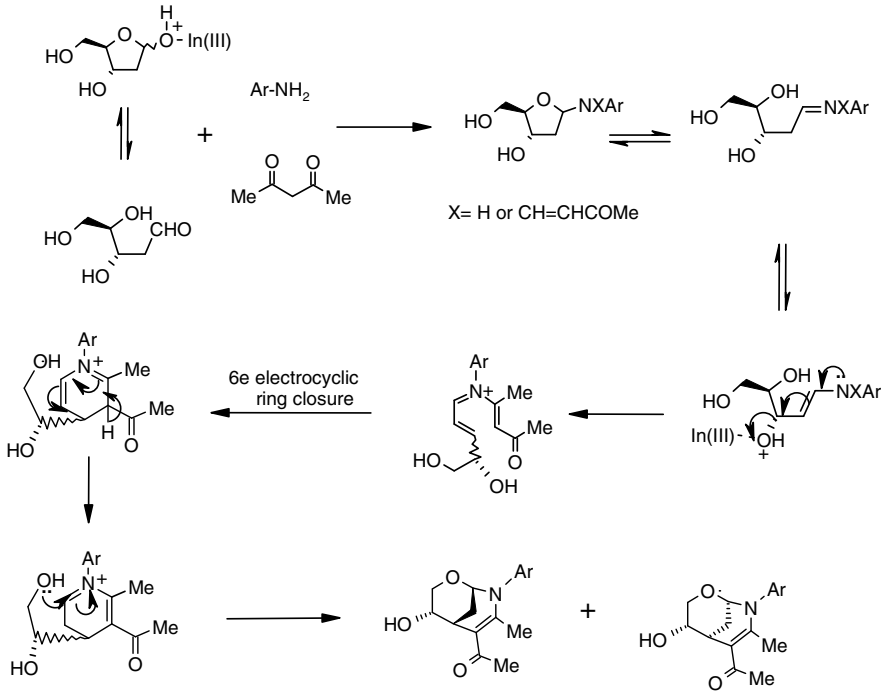


Fig. 3. X-ray crystal structure of **5c**.



Scheme 3. A plausible reaction mechanism.

This result provided the incentive for further study of reactions with various other aryl amines and lactols. Interestingly, a wide range of aryl amines including *ortho*-, *meta*-, and *para*-substituted anilines participated well in this reaction. As seen from Table 1, methoxy-substituted aryl amines gave comparatively higher yields than halogen-substituted aromatic amines. However, the reaction did not proceed with aliphatic amines under similar conditions because aliphatic amines are more basic and probably quench the Lewis acidity of $InCl_3$. Unlike alcohols and thiols, the aminoglycosidation with aliphatic amines is generally problematic even under drastic conditions. Furthermore, 2-deoxy-D-glucose and 2-deoxy-D-galactose failed to undergo cyclization with enamines to give the corresponding bicyclic aminols. Instead, both 2-deoxy-D-glucose and 2-deoxy-D-galactose underwent cyclodehydration in the presence of $InCl_3$ resulting in the formation of 2-furylethane-1,2-diol in 63% and 47% yields, respectively.[9] The scope and generality of this process is illustrated in Table 1.[11]

Simple lactols such as 2-hydroxytetrahydro-2*H*-pyran and 2-hydroxytetrahydrofuran failed to undergo cyclization with enamines. The solvent acetonitrile gave the best results. The effects of various indium(III) reagents such as InF_3, $InCl_3$, $In(ClO_4)_3$ and $In(OTf)_3$ were tested. Of these, indium trichloride was found to be the most effective catalyst in terms of conversion. Alternatively, 10 mol % of $InBr_3$ was found to be an equally effective catalyst for this conversion. A possible mechanism is depicted in Scheme 3.

In summary, we have described a direct one-pot procedure for the synthesis of sugar-derived bicyclic aminols involving a three-component coupling of 2-deoxyribose, acetyl acetone and aryl amines using a catalytic amount of $InCl_3$ under mild conditions. This method is quite simple and convenient to prepare a wide range of sugar-fused heterobicycles in a single step.

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8. Molecular mechanics calculations were carried out using the SYBYL 6.8 programme on a Silicon Graphics O2 workstation.
9. Babu, B. S.; Balasubramanian, K. K. *J. Org. Chem.* **2000**, *65*, 4198.
10. Compound **5c** was crystallized by slow evaporation from hexanes–dichloromethane (1:1); crystal data: $C_{19}H_{23}NO_5$, $M = 345.38$, orthorhombic, space group $P2_12_12_1$, $a = 8.0633(6)$ Å, $b = 12.7088(10)$ Å, $c = 17.2754(13)$ Å, $V = 1770.3(2)$ Å^3, $Z = 4$, $D_{calcd} = 1.296$ mg m^{-3}, $T = 294(2)$ K, $\mu = 0.094$ mm^{-1}, $F(000) = 736$, $\lambda = 0.71073$ Å. Data collection yielded 17,066 reflections resulting in 1809 unique, averaged reflections, 1746 with $I > 2\sigma(I)$. Full matrix least-squares refinement led to a final $R = 0.0297$, $wR = 0.0872$ and GOF = 1.054. Intensity data were measured on a Bruker Smart Apex with CCD area detector. Crystallographic data have been deposited for compound **5c** with the Cambridge Crystallographic Data Centre, [CCDC No. 675996]. Copies of the data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving. html or CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223 336 033; e-mail: deposit@ccdc.cam.ac.uk).
11. *General procedure*: A mixture of 2-deoxyribose (1 mmol), aniline (1 mmol), acetyl acetone (1 mmol) and $InCl_3$ (10 mol %) in acetonitrile (10 mL) was stirred at room temperature for the specified time required to complete the reaction (Table 1). After complete conversion, as indicated by TLC, the reaction mixture was diluted with water and extracted with ethyl acetate (2 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, concentrated in vacuo and purified by column chromatography on Silica Gel (Merck, 100–200 mesh, ethyl acetate–hexane, 1:9) to afford the pure bicyclic aminol. Compound **4c**: solid, mp 132–134 °C; $[\alpha]_D^{20}$ −214 (*c* 1.0, MeOH); IR (KBr): ν_{max} 2924, 2852, 1739, 1635, 1509, 1483, 1372, 1238, 1039, 957, 840 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.05 (d, $J = 9.0$ Hz, 2H, *ortho*), 6.91 (d, $J = 9.0$ Hz, 2H, *meta*), 5.13 (ddd, $J = 10.3$, 5.6, 4.4 Hz, 1H, H2), 4.94 (br t, $J = 3.0$ Hz, 1H, H5), 3.75–3.80 (m, 1H, H1$_{(pro\text{-}S)}$), 3.82 (s, 3H, OMe), 3.50–3.54 (m, 1H, H3), 3.40 (t, $J = 10.8$ Hz, 1H, H1$_{(pro\text{-}R)}$), 2.23 (dt, $J = 12.9$, 3.0 Hz, 1H, H4$_{(pro\text{-}R)}$), 2.25 (s, 3H, 10-Me), 2.18 (s, 3H, 6-Me), 2.03 (s, 3H, OAc), 1.91 (ddd, $J = 12.8$, 4.6, 2.2 Hz, 1H, H4$_{(pro\text{-}S)}$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 196.1, 169.8, 158.3, 154.9, 135.9, 128.7, 114.2, 106.2, 81.4, 70.7, 58.9, 55.0, 30.3, 29.4, 29.2, 27.9, 20.4, 19.7; ESI-MS: *m*/*z*: 368 (M+Na), 346 (M+H), 286, 242; HRMS calcd for $C_{19}H_{23}NO_5Na$ (M+Na): 368.1473. Found: 368.1460. Compound **5c**: solid, mp 156–158 °C; $[\alpha]_D^{20}$ +254 (*c* 1.0, MeOH); IR (KBr): ν_{max} 2924, 2852, 1739, 1635, 1509, 1483, 1372, 1238, 1039, 957, 840 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.05 (d, $J = 9.0$ Hz, 2H, *ortho*), 6.91 (d, $J = 9.0$ Hz, 2H, *meta*), 4.99 (br s, 1H, H5), 4.70 (br s, 1H, H2), 3.83 (s, 3H, OMe), 3.77–3.82 (m, 2H, H1), 3.25 (br s, 1H, H3), 2.51 (dt, $J = 12.6$, 3.0 Hz, 1H, H4$_{(pro\text{-}S)}$), 2.36 (s, 3H, 10-Me), 2.21 (s, 3H, 6-Me), 2.17 (s, 3H, OAc), 1.62 (dt, $J = 12.6$, 3.2 Hz, 1H, H4$_{(pro\text{-}R)}$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 196.4, 170.6, 158.8, 156.8, 136.2, 129.1, 114.6, 106.8, 83.0, 70.0, 61.2, 55.4, 31.0, 29.6, 29.3, 24.7, 21.3, 19.9; ESI-MS: *m*/*z*: 368 (M+Na), 346 (M+H), 286, 242, 226; HRMS calcd for $C_{19}H_{23}NO_5Na$ (M+Na): 368.1473. Found: 368.1478. Compound **4i**: solid, mp 151–153 °C; $[\alpha]_D^{20}$ −128, (*c* 1.0, MeOH); IR (KBr): ν_{max} 2950, 1724, 1630, 1517, 1438, 1379, 1298, 1241, 1196, 1121, 1039, 858, 771, 729, 671 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.20–7.28 (m, 3H, Ar-H), 7.04–7.12 (m, 1H, Ar-H), 5.10 (ddd, $J = 10.2$, 5.6, 4.4 Hz, 1H), 4.65 (br s, 1H), 3.77–3.88 (m, 1H), 3.40–3.58 (m, 2H), 2.21–2.25 (m, 1H), 2.20 (s, 3H), 2.18 (s, 3H), 2.06 (s, 3H), 2.02 (s, 3H), 1.90 (ddd, $J = 12.6$, 4.4, 2.1 Hz, 1H); ^{13}C NMR, (75 MHz, $CDCl_3$): δ 197.6, 170.6, 155.6, 142.2, 135.9, 131.5, 129.7, 128.6, 127.4, 106.0, 80.8, 71.6, 59.9, 31.0, 30.2, 28.4, 21.3, 19.6, 17.9; ESI-MS: *m*/*z*: 352 (M+Na), 330 (M+H), 226; HRMS calcd for $C_{19}H_{23}NO_4Na$ (M+Na): 352.1524. Found: 352.1511. Compound **5i**: solid, mp 188–190 °C; $[\alpha]_D^{20}$ +210, (*c* 1.0, MeOH); IR (KBr): ν_{max} 2924, 2858, 1737, 1637, 1522, 1434, 1375, 1335, 1241, 1193, 1143, 1050, 966, 870, 766 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.20–7.29 (m, 3H, Ar-H), 7.02–7.08 (m, 1H, Ar-H), 4.72 (br s, 2H), 3.70–3.94 (m, 2H), 3.25 (br s, 1H), 2.50 (dt, $J = 12.4$, 3.0 Hz, 1 H), 2.35 (s, 3H), 2.16 (s, 6H), 2.10 (s, 3H), 1.60 (dt, $J = 12.6$, 3.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 196.2, 170.6, 156.8, 141.7, 135.4, 131.2, 129.6, 128.3, 127.1, 106.0, 84.2, 81.6, 70.0, 61.3, 30.9, 29.3, 24.4, 21.3, 18.8; ESI-MS: *m*/*z*: 352 (M+Na), 330 (M+H), 270, 242, 226; HRMS calcd for $C_{19}H_{23}NO_4Na$ (M+Na): 352.1524. Found: 352.1511.