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Tetrahedron: *Asymmetry*

The stereoselective synthesis of nopinone based triazole ketones

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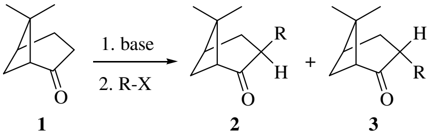
Abstract—The aldol reaction of nopinone **1** with triazole aldehydes followed by reduction with Zn/$ZnCl_2$ furnished isomers **2a**–**d** in satisfactory overall yields and excellent diastereoselectivities (ca 94% de).

1. Introduction

Triazoles represent an interesting class of compounds having a wide spectrum of biological properties.[1] Among them, some triazole substituted ketones are attractive target molecules because of their importance such as antifungal agents,[2] germicides[3] and antibacterials[4] including activities against tuberculosis.[5] The asymmetric synthesis of triazole substituted ketone merits attention since the absolute configuration of the alpha position to the carbonyl plays an important role for the antifungal activity.[2a]

Due to our continuing interest on the use of pinenes in asymmetric synthesis,[6] we focused on the stereoselective synthesis of novel (+)-nopinone based triazole ketones with potential biological activities.

The alkylation of the enolate of (+)-nopinone **1** with alkyl halides is reported to lead to a mixture of **2** and **3** usually favouring the thermodynamic diastereomer **2** (Scheme 1),[7] which was obtained in one case as the sole product by an aldol reaction of **1** with PhCHO followed by hydrogenation.[8] Conversely the monoalkylation of the lithium enolate of **1** with alkyl halides under kinetic conditions was reported to furnish isomers **3** in excellent diastereoselectivities.[9]

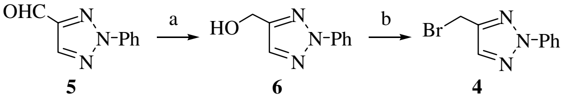


Scheme 1. Thermodynamic and kinetic alkylations of (+)-nopinone **1**.

Herein we report that, in contrast to the literature precedent,[9a,b] the kinetic alkylation of the lithium enolate of **1** with triazole bromide **4** gives product **2**, which was obtained in excellent diastereoselectivities from the aldol pathway.

2. Results and discussion

The 1,2,3-triazole bromide **4** was prepared from aldehyde **5**, a readily available derivative of D-(+)-glucose (Scheme 2).[10] Reduction of **5** with $NaBH_4$ furnished alcohol **6**,[11] which upon treatment with PBr_3 in ethyl ether gave **4**.[12]



Scheme 2. Reagents and conditions: (a) $NaBH_4$, MeOH, 10 min, 94%; (b) PBr_3, Et_2O, 24 h, 90%.

In contrast to that described in the literature for the use of alkyl halides,[9a,b] the kinetic alkylation of the lithium enolate of **1**[13] with triazole bromide **4** at −45 °C in the presence of HMPA as additive following the typical experimental procedure[9a,b] led to product **2a**, which was obtained in poor yields and stereoselectivity (Table 1, entry 1).[14] At higher temperatures, compound **2a** was produced in similar yield and in better diastereoselectivity (entry 2).

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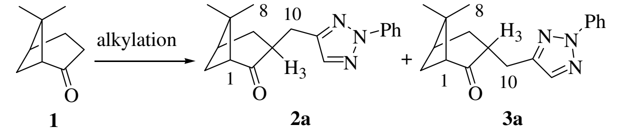
Table 1. Stereoselectivities in the alkylation of **1** with the bromide **4**



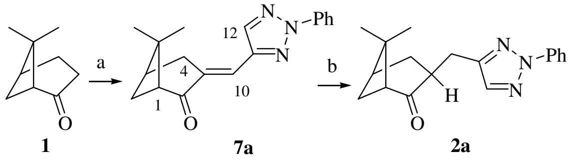
Entry	Reaction and conditions	%[a]	2a/3a[b]
1	LDA, THF, −10 °C then **4**, NaI, HMPA, −45 °C, 4 h	18	76:24
2	LDA, THF, −10 °C then **4**, NaI, HMPA, 0 °C, 1 h	24	87:13

[a] Yields for the purified mixture of products **2a** and **3a** by flash chromatography on silica gel.

[b] Ratios determined from the signals of both H_8 and H_{10} in the ^1H NMR spectra (300 MHz).

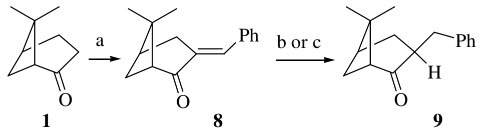
The **2a**/**3a** ratios were determined from the signals due to the hydrogens H_8, H_{10} and H_{12} in the ^1H NMR spectra at 300 MHz of these crude mixtures. The stereochemical assignment of the newly created stereogenic centre in the main isomer **2a** was made on the basis of NOE NMR spectrum as already described in the literature for a related compound.[8] Indeed, starting from H_8, significant NOE was observed with $H_{4\beta}$ (2.3%). Also observed were NOEs of $H_{4\alpha}$ with H_3 (7.7%) and of H_3 with $H_{7\alpha}$ (4.6%), which implies a *syn* relationship between the methylene-triazole appendage and the gem-dimethylene bridge of the pinane moiety. Also noteworthy, the NOE between H_8 and H_{10} was not observed while a strong NOE of H_3 with H_{10} (9.1%) suggests for isomer **2a** a preferred conformation in which the hydrogens H_8 and H_{10} are not close together.

The aldol pathway proved to be a very attractive route to isomer **2a** in high diastereoselectivity (Scheme 3). The aldol condensation of **1** with aldehyde **5** was carried out following the typical procedure[8] giving enone **7a** as a single geometric isomer.[15] The assignment of the configuration of the double bond was made on the basis of NOE NMR spectrum. Neither $H_{4\alpha}$ nor $H_{4\beta}$ gave NOE with H_{10}. However H_4 showed a strong NOE with H_{12} (8.4%) allowing us to define the geometry of the double bond. Since hydrogenation of **7a** in Pd/C and in Pt failed, this compound was converted to **2a** upon treatment with the system $Zn/ZnCl_2$.[16,17] The **2a**/**3a** = 97:3 ratio was obtained from the signals of H_8, H_{10} and H_{12} in the crude ^1H NMR spectrum while the stereochemistry at the 3-position was determined on the basis of NOE experiments, as reported above for the alkylation of **1**.



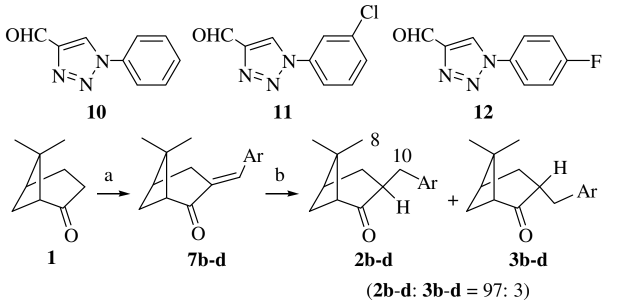
Scheme 3. Reagents and conditions: (a) **5** (1 equiv), aq KOH, reflux, 20 h, 56%; (b) Zn, $ZnCl_2$, EtOH, reflux, 2 h, 92%.

The catalytic hydrogenation of enone **8** derived from **1** was reported to furnish stereoselectively the *exo*-isomer **9**.[8] Reduction of **8** with $Zn/ZnCl_2$ gave **9** in an *exo*/*endo* = 97:3 ratio. The specific rotation of **9** thus obtained was compared with the product reported by hydrogenation of **8**,[8] showing that these methodologies occur with the same stereochemical sense (Scheme 4).



Scheme 4. Reagents and conditions: (a) see Ref. 8; (b) see Ref. 8: H_2, Pd/C, AcOEt, 95%, $[\alpha]_D^{20} = -56.4$ (*c* 1.6, EtOH); (c) Zn, $ZnCl_2$, EtOH, reflux, 2 h, 93%, $[\alpha]_D^{20} = -50$ (*c* 1.6, EtOH).

In order to verify the scope of this stereochemical course producing mainly isomers **2**, the already known triazole aldehydes **10**–**12**[18] were employed in the aldol pathway (Scheme 5). Thus, the aldol reactions of **1** with **10**–**12** furnished the corresponding enones **7b**–**d** as single isomers,[19–21] which were reduced with the $Zn/ZnCl_2$ system in EtOH to the respective compounds **2b**–**d** in good yields and diastereoselectivities (*exo*/*endo* = 97:3).[22–24] Also here the epimeric **2b**–**d**/**3b**–**d** ratios at the 3-position were obtained from the signals of H_8 and H_{12} in the crude ^1H NMR spectra while the absolute configurations at the 3-position were made from NOE spectra as reported for the alkylation of **1**.



Scheme 5. Reagents and conditions: (a) **10** or **11** or **12** (1 equiv), aq KOH, reflux, 20 h (**7b**: 55%, **7c**: 58%, **7d**: 59%); (b) Zn, $ZnCl_2$, EtOH, reflux, 2 h (**2b**: 75%, **2c**: 70%, **2d**: 80%).

3. Conclusion

In summary, the aldol pathway for the introduction of methylenetriazole moieties in nopinone **1** furnishing the isomers **2a**–**d** in high stereoselectivities (ca 94% de), is an attractive and complementary protocol to the already reported kinetic alpha alkylation of the lithium enolate of **1**,[9a,b] which was shown to be inefficient for the alkylation with triazole bromide **4**.

Acknowledgements

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10. Hann, M. R.; Hudson, C. S. *J. Am. Chem. Soc.* **1944**, *66*, 735–738.
11. Alcohol **6**: White solid, mp 64–65 °C. IR (KBr, cm^{-1}): 3317, 3232, 2943, 1595, 1489, 1414, 1353, 1306, 1050, 1014, 964, 849, 760, 730. ^{1}H NMR (300 MHz, CDCl$_3$, ppm): 8.05 (ddd, 7.2, 3.0, 1.2 Hz, CH), 7.80 (s, CH), 7.48 (ddd, 7.5, 7.2, 1.8 Hz, CH), 7.35 (tt, 7.5, 1.2 Hz, CH), 4.88 (d, 5.6 Hz, CH$_2$), 1.98 (t, 5.6 Hz, OH).
12. Compound **4**: White solid after flash chromatography on silica gel (10% AcOEt in hexane as eluant), mp 44-45 °C. IR (KBr, cm^{-1}): 3036, 1594, 1498, 1487, 1341, 1333, 1212, 1034, 966, 859, 760, 737, 711. ^{1}H NMR (300 MHz, CDCl$_3$, ppm): 8.07 (ddd, 7.3, 3.2, 1.2 Hz, CH), 7.82 (s, CH), 7.46 (ddd, 7.5, 7.3, 1.6 Hz, CH), 7.36 (tt, 7.5, 1.2 Hz, CH), 4.61 (s, CH$_2$).
13. (+)-Nopinone is available from Aldrich Chem. Co.
14. Mixture of isomers **2a** and **3a**: Pale yellow oil after flash chromatography on silica gel (1% AcOEt in hexane as eluant). $[\alpha]_D^{25} = -27.0$ (*c* 0.63, CH$_2$Cl$_2$) for **2a**/**3a** = 76:24. ^{1}H NMR (300 MHz, CDCl$_3$, ppm): 8.03 (ddd, 7.2, 3.0, 1.2 Hz, H-14), 7.66 (s, H-12 of **2a**), 7.62 (s, H-12 of **3a**), 7.46 (ddd, 7.5, 7.2, 1.8 Hz, H-15), 7.32 (tt, 7.5, 1.2 Hz, H-16), 3.52 (dd, 15.0, 4.2 Hz, H-10 of **2a**), 3.41 (dd, 13.5, 4.5 Hz, H-10 of **3a**), 3.10–3.00 (m, H-3 of **2a**), 2.89–2.81 (m, H-3 of **3a**), 2.94 (dd, 16.5, 4.5 Hz, H-10 of **3a**), 2.72 (dd, 15.0, 9.6 Hz, H-10 of **2a**), 2.66 (dd, 5.4, 5.1 Hz, H-1), 2.59-2.53 (m, H-7β of **3a**), 2.52–2.45 (m, H-7β of **2a**), 2.33 (ddd, 13.2, 10.2, 4.8 Hz, H-4α), 2.27 (ddd, 5.4, 5.1, 4.8 Hz, H-5), 1.76 (d, 10.5 Hz, H-7α), 1.71–1.64 (m, H-4β), 1.34 (s, H-9 of **2a**), 1.33 (s, H-9 of **3a**), 0.94 (s, H-8 of **3a**), 0.75 (s, H-8 of **2a**). ^{13}C NMR (CDCl$_3$, ppm): 215.0 (C-2), 148.0 (C-11), 139.8 (C-13), 134.8 (C-12), 129.6 (C-15), 126.8 (C-16), 118.4 (C-14), 58.5 (C-1 of **3a**), 57.6 (C-1 of **2a**), 43.2 (C-6), 42.4 (C-3), 41.6 (C-5), 31.5 (C-4 of **3a**), 28.6 (C-4 and C-7 of **2a**), 28.2 (C-7 of **3a**), 25.9 (C-10 of **3a**), 25.4 (C-10 of **2a**), 26.1 (C-9), 21.9 (C-8).
15. Compound **7a**: White solid after flash chromatography on silica gel (10% AcOEt in hexane as eluant), mp 63–64 °C. $[\alpha]_D^{25} = -1.8$ (*c* 2.65, CH$_2$Cl$_2$). IR (KBr, cm^{-1}): 3084, 2932, 1698, 1624, 1597, 1499, 1463, 1213, 1198, 1063, 965, 756, 690, 666. ^{1}H NMR (300 MHz, CDCl$_3$, ppm): 8.13 (ddd, 7.2, 3.0, 1.3 Hz, H$_{arom}$), 7.97 (s, H-12), 7.76 (t, 2.6 Hz, H-10), 7.51 (ddd, 7.5, 7.2, 1.8 Hz, H$_{arom}$), 7.38 (tt, 7.5, 1.2 Hz, H$_{arom}$), 3.15 (ddd, 18.0, 2.7, 2.4 Hz, H-4α), 3.05 (dddd, 18.0, 2.4, 2.3, 2.1 Hz, H-4β), 2.75 (dd, 5.7, 5.6 Hz, H-1), 2.69 (dddd, 10.2, 6.0, 5.6, 2.1 Hz, H-7β), 2.46–2.40 (m, H-5), 1.55 (d, 10.2 Hz, H-7α), 1.41 (s, H-9), 0.94 (s, H-8). ^{13}C NMR (CDCl$_3$, ppm): 198.0 (C-2), 140.4 (C-11), 135.2 (C-13), 132.7 (C-12), 131.2 (C-3), 124.8 (C-15), 123.4 (C-16), 118.0 (C-10), 114.3 (C-14), 51.7 (C-1), 36.4 (C-6), 34.6 (C-5), 27.0 (C-4), 23.3 (C-7), 21.8 (C-9), 17.2 (C-8). MS (70 eV, *m/z*): 294 (M + 1, 16), 293 (M^+, 77), 278 (41), 250 (100), 91 (29), 77 (36). HREIMS calcd for $C_{18}H_{19}N_3O$ (M^+): 293.1528. Found: 293.1506.
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17. Compound **2a** in a 94% de: pale yellow oil by flash chromatography on silica gel (3% AcOEt in hexane as eluant). $[\alpha]_D^{25} = -46.0$ (*c* 0.76, CH$_2$Cl$_2$). IR (neat, cm^{-1}): 3053, 2927, 2870, 1705, 1598, 1519, 1500, 1463, 1348, 1201, 1038, 1024, 965, 852, 757, 691, 665. ^{1}H NMR (300 MHz, CDCl$_3$, ppm): 8.03 (ddd, 7.2, 3.0, 1.2 Hz, H-14), 7.66 (s, H-12), 7.46 (ddd, 7.5, 7.2, 1.8 Hz, H-15), 7.32 (tt, 7.5, 1.2 Hz, H-16), 3.52 (dd, 15.0, 4.2 Hz, H-10), 3.10–3.00 (m, H-3), 2.72 (dd, 15.0, 9.6 Hz, H-10), 2.66 (dd, 5.4, 5.1 Hz, H-1), 2.52–2.45 (m, H-7β), 2.33 (ddd, 13.2, 10.2, 4.8 Hz, H-4α), 2.27 (ddd, 5.4, 5.1, 4.8 Hz, H-5), 1.76 (d, 10.5 Hz, H-7α), 1.71–1.64 (m, H-4β), 1.34 (s, H-9), 0.75 (s, H-8). ^{13}C NMR (CDCl$_3$, ppm): 215.0 (C-2), 148.0 (C-11), 139.8 (C-13), 134.8 (C-12), 129.6 (C-15), 126.8 (C-16), 118.4 (C-14), 57.6 (C-1), 43.2 (C-6), 42.4 (C-3), 41.6 (C-5), 28.6 (C-4 and C-7), 25.4 (C-10), 26.1 (C-9), 21.9 (C-8). MS (70 eV, *m/z*): 297 (M + 2, 14), 296 (M + 1, 66), 295 (M^+, 100), 254 (25), 226 (94), 185 (36), 171 (28), 159 (84), 158 (47), 137 (29), 103 (33), 95 (30), 91 (62), 83 (56), 77 (53), 55 (32). HREIMS calcd for $C_{18}H_{21}N_3O$ (M^+): 295.0366. Found: 295.0351.
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19. Compound **7b**: White solid after flash chromatography on silica gel (10% AcOEt in hexane as eluant), mp 168–169 °C. $[\alpha]_D^{25} = +5.5$ (*c* 2.3, CH$_2$Cl$_2$). IR (KBr, cm^{-1}): 3175, 3001, 2963, 2929, 1691, 1613, 1597, 1500, 1467, 1369, 1305, 1215, 1200, 1059, 1045, 983, 808, 759, 688. ^{1}H NMR (300 MHz, CDCl$_3$, ppm): 8.14 (s, H-12), 7.78 (ddd, 7.2, 3.0, 1.2 Hz, H$_{arom}$), 7.81 (t, 2.4 Hz, H-10), 7.56 (ddd, 7.5, 7.2, 1.8 Hz, H$_{arom}$), 7.48 (tt, 7.2, 1.2 Hz, H$_{arom}$), 3.16 (ddd, 18.0, 2.6, 2.4 Hz, H-4α), 3.06 (dddd, 18.0, 2.6, 2.4, 2.1 Hz, H-4β), 2.73 (dd, 5.7, 5.6 Hz, H-1), 2.68 (dddd, 10.2, 6.1,

5.7, 2.1 Hz, H-7β), 2.44–2.38 (m, H-5), 1.55 (d, 10.2 Hz, H-7α), 1.40 (s, H-9), 0.93 (s, H-8). ^{13}C NMR (CDCl$_3$, ppm): 202.2 (C-2), 144.6 (C-11), 136.4 (C-13), 134.0 (C-3), 129.8 (C-15), 128.9 (C-16), 122.6 (C-10), 122.4 (C-12), 120.4 (C-14), 55.9 (C-1), 41.0 (C-6), 39.3 (C-5), 31.2 (C-4), 27.8 (C-7), 26.1 (C-9), 21.7 (C-8). MS (70 eV, *m/z*): 293 (M$^+$, 3), 250 (10), 222 (43), 104 (38), 91 (17), 77 (100), 51 (29). HREIMS calcd for $C_{18}H_{19}N_3O$ (M$^+$): 293.1528. Found: 293.1481.

20. Compound **7c**: White solid after flash chromatography on silica gel (10% AcOEt in hexane as eluant), mp 143–144 °C. $[\alpha]_D^{25} = +2.5$ (*c* 2.29, CH$_2$Cl$_2$). IR (KBr, cm^{-1}): 3132, 2948, 1690, 1625, 1594, 1489, 1370, 1310, 1263, 1199, 1055, 1043, 984, 882, 797, 780, 678. ^{1}H NMR (300 MHz, CDCl$_3$, ppm): 8.14 (s, H-12), 7.81 (t, 2.0 Hz, H-10), 7.79 (t, 2.4 Hz, H$_{arom}$), 7.70 (dt, 7.8, 1.8 Hz, H$_{arom}$), 7.50 (t, 8.1 Hz, H$_{arom}$), 7.45 (ddd, 8.1, 1.8, 1.6 Hz, H$_{arom}$), 3.13 (ddd, 18.0, 2.7, 2.4 Hz, H-4α), 3.03 (dddd, 18.0, 2.4, 2.3, 2.1 Hz, H-4β), 2.74 (dd, 5.8, 5.6 Hz, H-1), 2.67 (dddd, 10.2, 6.0, 5.8, 2.1 Hz, H-7β), 2.44-2.39 (m, H-5), 1.54 (d, 10.2 Hz, H-7α), 1.41 (s, H-9), 0.93 (s, H-8). ^{13}C NMR (CDCl$_3$, ppm): 202.0 (C-2), 144.8 (C-11), 137.6 (C-15), 135.6 (C-13), 134.4 (C-3), 131.0 (C-17), 129.0 (C-16), 122.6 (C-14), 122.2 (C-12), 120.8 (C-10), 118.4 (C-18), 56.0 (C-1), 41.1 (C-6), 39.2 (C-5), 31.2 (C-4), 27.7 (C-7), 26.2 (C-9), 21.8 (C-8). MS (70 eV, *m/z*): 329 (M + 2, 3), 327 (M$^+$, 18), 299 (25), 298 (24), 264 (23), 258 (33), 256 (100), 228 (22), 193 (20), 154 (30), 138 (75), 111 (74), 91 (35), 75 (30), 55 (50). HREIMS calcd for $C_{18}H_{18}N_3ClO$ (M$^+$): 327.1138. Found: 327.1129.
21. Compound **7d**: White solid after flash chromatography on silica gel (10% AcOEt in hexane as eluant), mp 164–165 °C. $[\alpha]_D^{25} = +11.2$ (*c* 2.09, CH$_2$Cl$_2$). IR (KBr, cm^{-1}): 3168, 2934, 1734, 1688, 1610, 1518, 1368, 1310, 1234, 1198, 1060, 1046, 984, 840, 819, 770, 612. ^{1}H NMR (300 MHz, CDCl$_3$, ppm): 8.11 (s, H-12), 7.79 (t, 2.4 Hz, H-10), 7.76 (ddd, 9.3, 4.5, 2.1 Hz, H-14), 7.26 (ddd, 9.3, 8.1, 2.1 Hz, H-15), 3.14 (ddd, 18.0, 2.7, 2.4 Hz, H-4α), 3.04 (dddd, 18.0, 2.4, 2.3, 2.1 Hz, H-4β), 2.72 (dd, 5.7, 5.6 Hz, H-1), 2.68 (dddd, 10.2, 6.0, 5.7, 2.1 Hz, H-7β), 2.44–2.38 (m, H-5), 1.54 (d, 10.2 Hz, H-7α), 1.41 (s, H-9), 0.93 (s, H-8). ^{13}C NMR (CDCl$_3$, ppm): 202.1 (C-2), 164.2 (C-11), 161.0 (C-16), 145.0 (C-13), 134.0 (C-3), 124.4 (C-10 and C-14), 122.3 (C-12), 116.9 (C-15), 56.0 (C-1), 41.0 (C-6), 39.3 (C-5), 31.2 (C-4), 27.8 (C-7), 26.1 (C-9), 21.7 (C-8). MS (70 eV, *m/z*): 311 (M$^+$, 7), 283 (36), 268 (31), 240 (95), 212 (28), 172 (31), 122 (100), 95 (99), 91 (38), 55 (32). HREIMS calcd for $C_{18}H_{18}N_3FO$ (M$^+$): 311.1434. Found: 311.1432.
22. Compound **2b** (**2b**/**3b** = 97:3): White solid after flash chromatography on silica gel (3% AcOEt in hexane as eluant), mp 85–86 °C. $[\alpha]_D^{25} = -10.8$ (*c* 1.11, CH$_2$Cl$_2$). IR (KBr, cm^{-1}): 3131, 3086, 2950, 2925, 2870, 1706, 1599, 1503, 1226, 1198, 1047, 768, 695. ^{1}H NMR (300 MHz, CDCl$_3$, ppm): 7.88 (s, H-12 of **2b**), 7.80 (s, H-12 of **3b**), 7.72 (ddd, 7.2, 3.0, 1.2 Hz, H-14), 7.51 (ddd, 7.5, 7.2, 1.8 Hz, H-15), 7.42 (tt, 7.5, 1.2 Hz, H-16), 3.46 (dd, 15.0, 4.2 Hz, H-10 of **2b**), 3.38 (dd, 14.3, 4.0 Hz, H-10 of **3b**), 3.17–3.03 (m, H-3), 2.91 (dd, 9.9, 4.2 Hz, H-10 of **3b**), 2.81 (dd, 15.0, 9.6 Hz, H-10 of **2b**), 2.63 (dd, 5.3, 5.1 Hz, H-1), 2.51-2.44 (m, H-7β), 2.37 (ddd, 13.2, 10.0, 4.6 Hz, H-4α), 2.29–2.21 (m, H-5), 1.76 (d, 10.5 Hz, H-7α), 1.72 (dd, 13.2, 7.8 Hz, H-4β), 1.34 (s, H-9 of **2b**), 1.33 (s, H-9 of **3b**), 0.94 (s, H-8 of **3b**), 0.70 (s, H-8 of **2b**). ^{13}C NMR (CDCl$_3$, ppm): 215.0 (C-2), 146.8 (C-11), 137.2 (C-13), 129.6 (C-15), 128.2 (C-16), 120.2 (C-12 and C-14), 57.6 (C-1), 43.2 (C-10), 42.4 (C-3), 41.6 (C-5), 39.8 (C-6), 28.6 (C-4), 26.1 (C-9), 25.4 (C-7), 21.9 (C-8). MS (70 eV, *m/z*): 295 (M$^+$, 3), 198 (23), 130 (100), 104 (59), 77 (93), 55 (22). HREIMS calcd for $C_{18}H_{21}N_3O$ (M$^+$): 295.0476. Found: 295.0498.
23. Compound **2c** (**2c**/**3c** = 97:3): White solid after flash chromatography on silica gel (3% AcOEt in hexane as eluant), mp 81–82 °C. $[\alpha]_D^{25} = -11.1$ (*c* 0.99, CH$_2$Cl$_2$). IR (neat, cm^{-1}): 3131, 3064, 2924, 2870, 1706, 1595, 1496, 1440, 1225, 1199, 1078, 1042, 804, 781, 770, 686. ^{1}H NMR (300 MHz, CDCl$_3$, ppm): 7.88 (s, H-12 of **2c**), 7.80 (s, H-12 of **3c**), 7.78 (dd, 2.1, 1.9 Hz, H-14), 7.63 (ddd, 7.8, 2.1, 1.5 Hz, H-18), 7.45 (t, 7.8 Hz, H-17), 7.41 (ddd, 7.8, 2.1, 1.5 Hz, H-16), 3.44 (dd, 15.0, 5.1 Hz, H-10 of **2c**), 3.37 (dd, 15.0, 6.0 Hz, H-10 of **3c**), 3.16–3.03 (m, H-3), 2.90 (dd, 15.0, 5.8 Hz, H-10 of **3c**), 2.81 (dd, 15.0, 7.9 Hz, H-10 of **2c**), 2.63 (t, 5.1 Hz, H-1), 2.52–2.44 (m, H-7β), 2.37 (ddd, 13.0, 10.0, 4.8 Hz, H-4α), 2.30–2.22 (m, H-5), 1.76 (d, 10.5 Hz, H-7α), 1.71 (dd, 13.0, 7.8 Hz, H-4β), 1.34 (s, H-9 of **2c**), 1.33 (s, H-9 of **3c**), 0.93 (s, H-8 of **3c**), 0.70 (s, H-8 of **2c**). ^{13}C NMR (CDCl$_3$, ppm): 214.9 (C-2), 147.0 (C-11), 137.8 (C-15), 135.3 (C-13), 130.6 (C-17), 128.4 (C-16), 120.4 (C-14), 120.2 (C-12), 118.1 (C-18), 58.2 (C-1 of **3c**), 57.5 (C-1 of **2c**), 43.3 (C-6), 42.4 (C-3), 40.6 (C-5 of **2c**), 40.0 (C-5 of **3c**), 28.6 (C-4 of **2c**), 28.2 (C-4 of **3c**), 26.2 (C-9 of **2c**), 26.0 (C-9 of **3c**), 25.2 (C-7), 25.1 (C-10), 21.7 (C-8). MS (70 eV, *m/z*): 329 (M$^+$, 2), 232 (20), 164 (100), 138 (64), 111 (68), 75 (30), 55 (36). HREIMS calcd for $C_{18}H_{20}N_3ClO$ (M$^+$): 329.1646. Found: 329.1672.
24. Compound **2d** (**2d**/**3d** = 97:3): White solid after flash chromatography on silica gel (3% AcOEt in hexane as eluant), mp 82–83 °C. $[\alpha]_D^{25} = -9.7$ (*c* 1.03, CH$_2$Cl$_2$). IR (neat, cm^{-1}): 3131, 3080, 2971, 2937, 2872, 1700, 1517, 1456, 1227, 1047, 839, 817. ^{1}H NMR (300 MHz, CDCl$_3$, ppm): 7.85 (s, H-12 of **2d**), 7.80 (s, H-12 of **3d**), 7.70 (ddd, 6.8, 4.5, 2.4 Hz, H-14), 7.22 (ddd, 8.1, 6.8, 2.4 Hz, H-15), 3.44 (dd, 15.0, 5.1 Hz, H-10 of **2d**), 3.37 (dd, 15.0, 6.0 Hz, H-10 of **3d**), 3.18–3.03 (m, H-3), 2.91 (dd, 9.0, 4.5 Hz, H-10 of **3d**), 2.83 (dd, 15.0, 7.9 Hz, H-10 of **2d**), 2.63 (t, 5.1 Hz, H-1), 2.52-2.44 (m, H-7β), 2.39 (ddd, 13.2, 10.2, 4.8 Hz, H-4α), 2.29–2.23 (m, H-5), 1.77 (d, 10.5 Hz, H-7α), 1.72 (dd, 13.2, 7.8 Hz, H-4β), 1.34 (s, H-9 of **2d**), 1.33 (s, H-9 of **3d**), 0.94 (s, H-8 of **3d**), 0.69 (s, H-8 of **2d**). ^{13}C NMR (CDCl$_3$, ppm): 215.0 (C-2), 163.7 (C-11), 160.4 (C-16), 146.8 (C-13), 122.2 (C-14 of **2d**), 122.1 (C-14 of **3d**), 120.4 (C-12 of **2d**), 120.3 (C-12 of **3d**), 116.6 (C-15 of **3d**), 116.3 (C-15 of **2d**), 58.1 (C-1 of **3d**), 57.5 (C-1 of **2d**), 43.2 (C-3 of **3d**), 42.4 (C-3 of **2d**), 40.7 (C-5 of **3d**), 40.6 (C-5 of **2d**), 28.6 (C-4 of **2d**), 28.2 (C-4 of **3d**), 26.2 (C-9 of **2d**), 26.0 (C-9 of **3d**), 25.2 (C-7), 25.1 (C-10), 21.8 (C-8 of **3d**), 21.7 (C-8 of **2d**). MS (70 eV, *m/z*): 314 (M + 1, 1), 313 (M$^+$, 2), 216 (20), 149 (51), 148 (100), 122 (51), 95 (33). HREIMS calcd for $C_{18}H_{20}N_3FO$ (M$^+$): 313.3512. Found: 313.3506.