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The reactivity of *N*-tosylphenylaziridine versus *N*-tosylphenylazetidine in heterocyclization reactions

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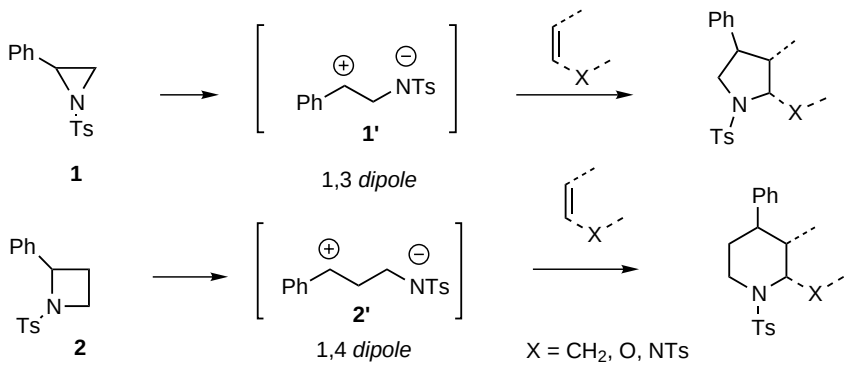
Abstract—*N*-Tosylaziridine (**1**) and *N*-tosylazetidine (**2**) react as 1,3 and 1,4 masked dipoles with electron rich alkenes, respectively, either under kinetic or thermodynamic control. The reactivity of the new aza oxo [4.4.0] **9**, a precursor of *N*-tosyliminium, was exploited for the preparation of stereodefined substituted piperidines.

The development of methods for the preparation of pyrrolidines or piperidines remains an area of current interest due to the presence of such saturated heterocyclic rings in a large number of biologically important compounds.[1–3] Therefore, new synthetic strategies for the rapid construction of these skeletons are of importance. Among the known methods for the preparation of heterocycles, cycloadditions seem to present the best compromise between efficiency and atom economy.[4] Recently we disclosed a new entry to pyrrolidines or piperidines via the use of *exo* stabilized 1,3 (**1′**) or 1,4 (**2′**) dipoles generated, respectively, from aziridine **1** or azetidine **2**. This provides an easy access to pyrrolidines or piperidines by formal [3+2] or [4+2] cycloadditions, using various activated or non activated dipole acceptors (Scheme 1).[5,6] In this letter we report new results concerning the reactivity of **1** and **2** as masked dipoles,[7] as well as some chemical transformations of the so-obtained cycloadducts.

In earlier experiments we found that the best conditions to produce either dipole **1′** or **2′**, respectively, from **1** or **2**, were to perform the reaction in CH_2Cl_2 in the presence of $BF_3{\cdot}Et_2O$. The transient dipoles in which the benzylic carbocation and the sulphonamide anion are the electrophilic and nucleophilic centers, respectively, can then be trapped with various alkenes.[5,6] However, evidence for a distinct reactivity pattern of aziridine **1** and azetidine **2** was rapidly apparent in considering the results with DHP (**3**) (compare entries 1 and 4 in Table 1). With aziridine **1**, a 1/1 mixture of cycloadducts aza-oxo [4.3.0], **6a**/**6b** was obtained, suggesting that the reaction was under kinetic control



Scheme 1.

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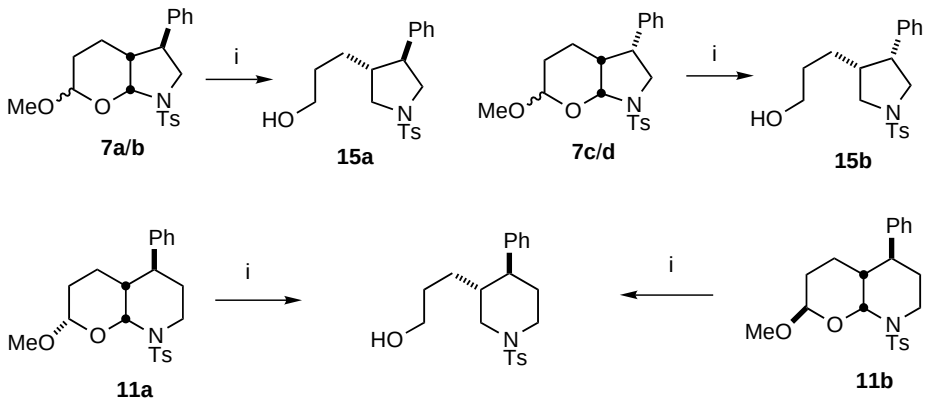
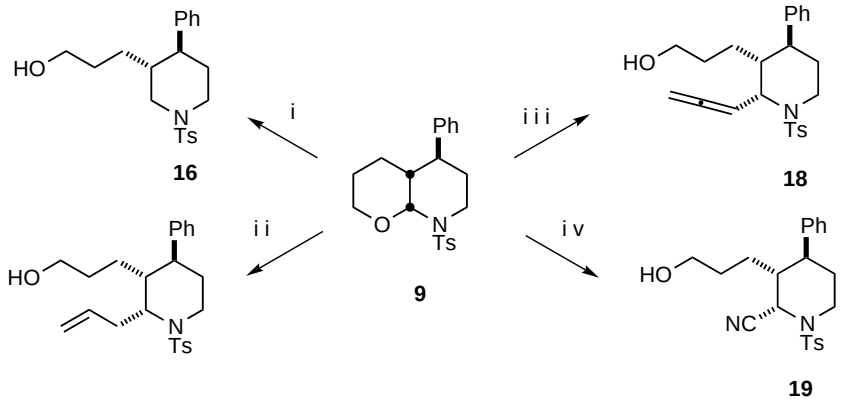
(entry 1). We confirmed experimentally that neither **6a** (*exo*-adduct) nor **6b** (*endo*-adduct) equilibrate under the reaction conditions. In contrast, bicyclic adduct **9a** was obtained after the reaction of azetidine (**2**) with DHP (**3**), identified as the *exo* diastereomer,[8] and the remaining material was a small amount of **9b**,[9] the *endo* adduct and the open chain tetrahydropyridine **10**, with a pyranyl appendage (entry 4). The formation of **10** is best explained by the evolution of a transient cycloadduct (we believe the unstable *endo* diastereomer) to an alcohol trapped by an excess of DHP present in the reaction mixture. Interestingly **10** could be cyclized to **9** under mild acidic conditions. Accordingly, the reactivity of **2** is probably controlled by a sequence of equilibria, suggesting a thermodynamic control of the reaction. However, if the anomeric effect is the stabilizing factor of cycloadduct **9**, the other possible cycloadducts might be unstable, and the tetrahydropyridine **10** will be the signature thereof.[10] In order to confirm and/or to exploit this finding we embarked on a systematic study with various and easily accessible electron rich alkenes such as **4** or **5**.[10] The reaction of **1** with **4** under the usual conditions gave a mixture of two sets of adducts **7a**/**7b** and **7c**/**7d**, which could be separated by careful chromatography (entry 2). NOESY experiments on each mixture showed that in **7a**/**7b** the phenyl ring is located in an *endo* position, whereas in **7c**/**7d** the phenyl ring is *exo*. Furthermore, we supposed that adducts **7a**/**7b** are α and β epimers at the acetal carbon. In order to clarify this point we submitted the two mixtures separately to reductive conditions (BCl_3, Et_3SiH, CH_2Cl_2, −78°C). The aminal/acetal functions were reduced permitting a chemical correlation to be made with the two pyrrolidines **15a** and **15b** from our previous work (Scheme 2).[6]

This sequence supports our assumption that **1** is reacting with **4** under kinetic control in giving all four possible diastereomers. In contrast the reaction of azetidine **2**[11] with **4** produces a complex mixture from which two compounds **11a** and **11b** could be extracted (entry 5). The aza,oxo bicycles **11a** and **11b**, epimeric at the acetal function, as assigned by NMR experiments, have probably an *exo* stereochemistry at the benzylic carbon. This assumption was reconfirmed by chemical correlations, performed by reductive opening of the oxygenated ring (see the transformation of **11a** and **11b** to **16** in Scheme 2). Aldehyde **11c** is probably the result of the instability of one set of bicyclic adducts (see above). The cycloaddition of **1** with tetrahydropyridine **5** (entry 3) was uneventful providing the corresponding cycloadducts **8a** and **8b**, separable by column chromatography on silica gel. Owing to the presence of atropisomerism at room temperature, the structural attribution from the 1D and 2D NMR spectra was possible at 330 K, and the compounds were clearly identified as the *exo* and *endo* epimers at the benzylic carbon. In contrast, the reaction of azetidine **2** with **5**

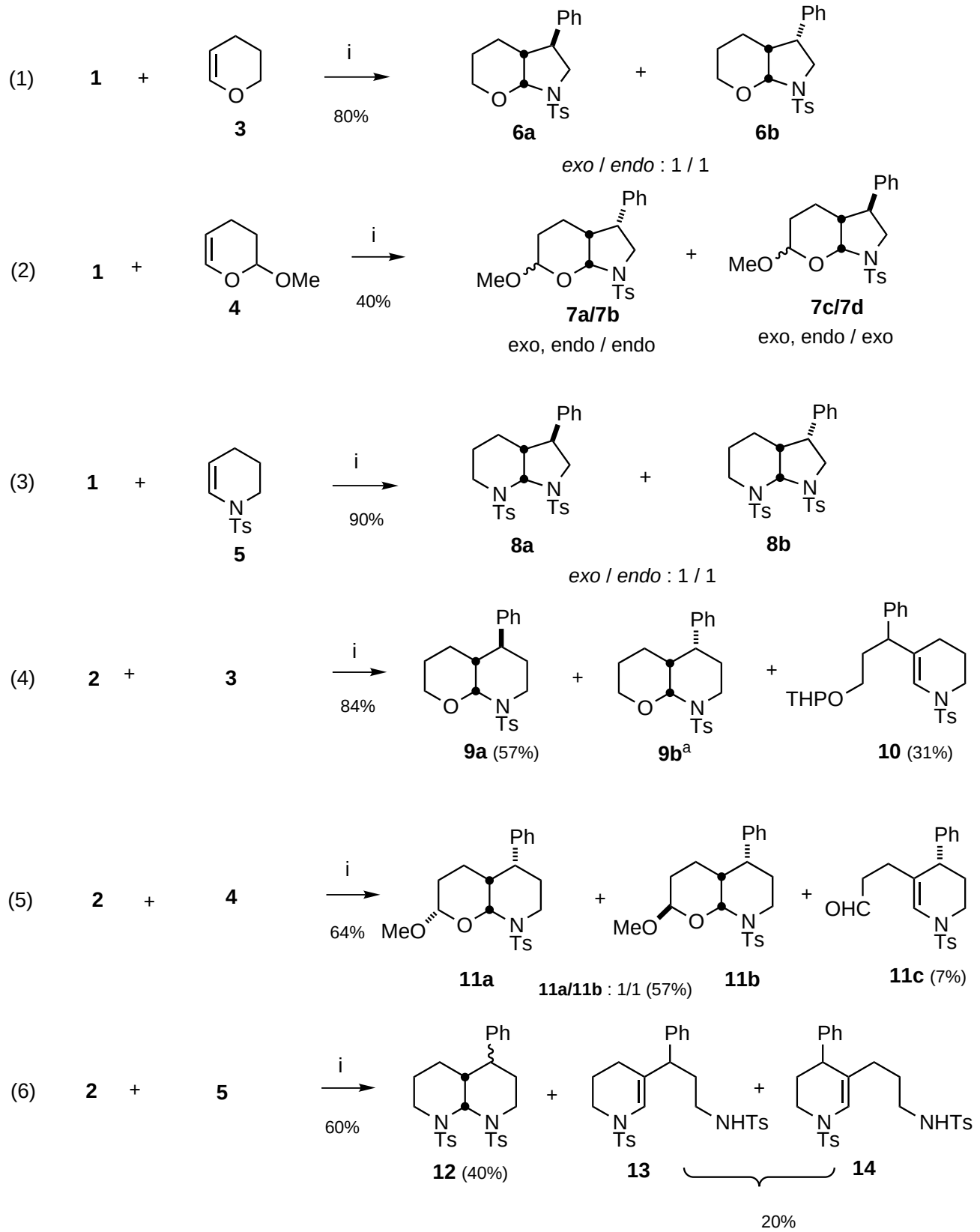


Scheme 2. *Reagents*: (i) Et_3SiH, BCl_3, CH_2Cl_2, −78°C (90–95%).



Scheme 3. *Reagents*: (i) Et_3SiH, BCl_3, CH_2Cl_2, −78°C, 95%; (ii) trimethyl-allylsilane, BF_3Et_2O, CH_2Cl_2, −78°C, 90%; (iii) propargylsilane, BF_3Et_2O, CH_2Cl_2, −78°C, 85%; (iv) TMSCN, BF_3Et_2O, CH_2Cl_2, −78°C, 84%.

Table 1.



Reagents: (i) BF_3Et_2O, CH_2Cl_2, −78°C; (ii) pTSA in toluene (95%). For the preparation of **1** and **2** see Refs. 5 and 11, respectively; compound **4** is commercially available. (a) see text and Ref. 9.

(entry 6) provided a complex mixture of products from which the expected cycloadduct **12** could be extracted, but whose stereochemistry could not be attributed owing to atropisomerism even at higher temperature. The isolated open chain tetrahydropyridines **13** and **14** clearly result from further evolution of initial cycloadducts by an iminium/enamine proton shift (entry 6).

Finally we would like to demonstrate that the [4.4.0] cycloadduct **9** is a valuable intermediate in order to obtain substituted piperidines (Scheme 3). Indeed, **9** is a direct precursor of a cyclic *N*-tosyliminium as shown by the following experiments.[12,13] A series of nucleophiles including Et_3SiH, trimethylallylsilane, TMSCN and propargylsilane were allowed to react with **9** in the presence of Lewis acids such as BCl_3 or $BF_3{\cdot}Et_2O$. In the case of Et_3SiH, reductive ring opening took place to yield the phenyl-piperidinol **16**. With trimethylallylsilane the opening of the pyranyl ring was observed: the nucleophilic allylsilane quenched the transient *N*-tosyliminium ion to realize allylation at C(2) yielding **17** as a single diastereomer. The stereochemistry of the newly formed stereocenter was assigned as *cis* by NOE experiments. Stereoelectronic considerations in six-membered rings favor the 'half-chair' over the corresponding 'twist' transition state (anti-parallel attack of the nucleophile),[14] but an anchimeric assistance from the tosyl group cannot be excluded. The reaction with propargylsilane and TMSCN were uneventful in yielding the corresponding allenyl and cyano adducts **18** and **19**, respectively, with a *cis* stereochemistry for the newly created stereocenter. The single-crystal X-ray structure of **19** comforts the NMR analysis of all the above piperidines.[15,16]

In this work, the reactivities of aziridine **1** and azetidine **2** towards electron rich olefins were compared. Aziridine **1** behaves as a 1,3 dipole in giving the [3+2] cycloadducts in a pathway that is probably under kinetic control. Azetidine **2** has a more complex behavior, in forming first the [4+2] cycloadducts which further evolve, suggesting a thermodynamic control of the reaction. Finally the synthetic potential of cycloadduct **9** was illustrated by the preparation of diastereomerically pure substituted piperidines.

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15. The X-ray structure and coordinates for compound **20** have been deposited at the Cambridge Crystallographic Database under the following code CCDC 142896. Crystal data for **19**: $C_{24}H_{29}NO_3S$, $M=411.57$, monoclinic, space group: $P2_{1/n}$, $a=11.6080(4)$, $b=16.4210(6)$, $c=12.6180(6)$, $U(Å^3)=2283$, $T=294$ K, $Z=4$, μ(Mo-Kα)$=0.165$ mm^{-1}, 24792 measured reflections, 2619 unique ($R_{int}=0.056$). The final $wR(F^2)$ was 0.057 (all data).
16. Selected physical data: Compound **8a**: ^{1}H NMR (300 MHz, $CDCl_3$, 330 K) δ (ppm): 7.91 (d, $J=8.5$ Hz, 2H), 7.86 (d, $J=8.2$ Hz, 2H), 7.48–7.11 (m, 7H), 6.88–6.71 (m, 2H), 5.81 (d, $J=7.2$ Hz, 1H), 3.96 (dd, 1H, $J=7.5$ and 10.3 Hz), 3.48–3.19 (m, 3H), 3.11 (dd, 1H, $J=6.9$ and 13.4 Hz), 2.46 (s, 3H), 2.42 (s, 3H), 2.22–2.11 (m, 1H), 1.75–1.41 (m, 4H). ^{13}C NMR (50 MHz, $CDCl_3$, 330 K) δ (ppm): 144.2, 143.9, 140.7, 137.5, 133.8, 130.2, 129.9, 129.2, 128.7, 128.5, 127.4, 127.3, 70.9, 53.7, 44.7, 43.7, 38.9, 22.8, 22.2 19.9.
Compound **8b**: ^{1}H NMR (300 MHz, $CDCl_3$, 330 K) δ (ppm): 8.01–7.95 (m, 4H), 7.42–7.19 (m, 7H), 7.11–6.95 (m, 2H), 5.84 (d,1H, $J=5.1$ Hz), 4.02 (dd, 1H, $J=11.$Hz) 3.81 (dd, 1H, $J=8.1$ and 11.1 Hz), 3.45 (d, 1H, $J=14$ Hz), 3.21–2.92 (m, 2H), 2.48 (s, 3H), 2.47 (s, 3H), 2.41–2.19 (m, 1H), 1.71–1.02 (m, 4H). ^{13}C NMR (50 MHz, $CDCl_3$, 330 K) δ (ppm): 144.3, 144, 137.4, 136.4, 134.1, 130.3, 130.1, 129, 128.7, 128.5, 127.8, 127.5, 72.1, 49.3, 43.4, 40.9, 40.4, 21.9, 21.5.
Compound **9**: ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.76 (ddd, 2H, $J=2$, 3.7 and 8.5 Hz), 7.38–7.35 (m, 5H), 7.11–7.16 (m, 2H), 5.37 (d, 1H, $J=2.5$ Hz), 3.89 (dd, 1H, $J=4.8$ and 11.4 Hz), 3.63 (dddd, 1H, $J=2.6$, 4.5 7.1 and 11.4 Hz), 3.56 (ddd, $J=1$, 2.5 and 12.5 Hz, 1H), 3.03 (ddd, $J=4.2$, 12 and 16.1 Hz), 2.91 (ddd, 1H, $J=3.4$, 11.9 and 15 Hz), 2.42 (s, 3H), 2.01 (m, 1H), 1.92 (ddd, $J=4.5$, 13 Hz, 17.6 Hz, 1H) 1.89–1.82 (m, 1H), 1.71–1.57 (m, 1H), 1.56–1.42 (m, 2H), 1.19–1.12 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 146.9, 143.8, 14.3.7, 136.7, 129.6, 129.6, 129.1, 128.6, 127.8, 127.1, 84.6, 68.3, 41.8, 40.8, 38.9, 33.8, 25.9, 21.9, 20.4.

Compound **16**: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.69 (d, 2H, $J=8.4$ Hz), 7.36 (d, 2H, $J=8.1$ Hz), 7.32–7.14 (m, 3H), 7.12–7.01 (m, 2H), 4.02 (dd, 1H, $J=1.9$ and 10 Hz,), 3.92–3.86 (m, 1H), 3.52–3.39 (m, 2H), 2.46 (s, 3H), 2.30 (ddd, 1H, $J=4.4$, 11.5 and 15.3), 2.13–1.72 (m, 5H), 1.61–1.4 (m, 1H), 1.32–1.15 (m, 2H), 1.02–0.83 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 143.8, 143.5, 133.9, 129.8, 128.8, 127.9, 127.6, 126.8, 62.8, 51.4, 48.8, 46.9, 40.7, 34.1, 29.7, 27.6, 21.5.

Compound **17**: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.79 (d, 2H, $J=8.3$ Hz), 7.41–7.05 (m, 5H), 6.95–6.33 (m, 2H), 5.82–5.65 (m, 1H), 5.13–4.97 (m, 2H), 4.29 (ddd, 1H, $J=4.2$, 9.3 and 15.3 Hz) 3.92–3.81 (m, 1H), 3.51–3.33 (m, 2H), 3.12–3.04 (m, 1H), 2.61–2.36 (m, 2H), 2.49 (s, 3H), 2.23–2.18 (m, 1H), 1.83–1.64 (m, 1H), 1.61–1.38 (m 3H), 1.22–1.13 (m, 1H), 1.06–0.88 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 144.1, 143.2, 139.1, 135.2 (C10) 129.8, 128.8, 127.4, 126, 116.9, 62.8, 54.9, 43.4, 42.8, 40.3, 33.4, 29.6, 29.1, 26.2, 21.7.

Compound **18**: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.72 (d, 2H, $J=8.4$ Hz), 7.39–7.18 (m, 5H), 7.13–7.02 (m, 2H), 5.12–5 (m, 1H), 4.89–4.81 (m, 1H), 4.72–4.58 (m, 2H), 3.92–3.86 (m, 1H), 3.3–3.36 (m, 2H), 3.03 (ddd, 1H, $J=4.7$, 12.8 and 15.9 Hz), 2.57–2.41 (m, 1H), 2.45 (s, 3H), 2.12–1.98 (m, 1H), 1.93–1.66 (m, 2H), 1.63–1.49 (m, 1H), 1.32–1.15 (m, 1H), 1.12–0.98 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 209.4, 143.8 143.2, 137.6 (Cq, ar.), 129.5, 128.8, 127.7, 127.6, 126.9, 82.9, 76.3, 62.9, 55.3, 45.2, 43.6, 41.2, 34.5, 29.7, 26.3, 21.7.

Compound **19**: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.72 (d, 2H, $J=8.4$ Hz), 7.21–7.18 (m, 5H), 7.13–7.02 (m, 2H), 5.12–5 (m, 1H), 4.89–4.81 (m, 1H), 4.72–4.58 (m, 2H), 3.92–3.86 (m, 1H), 3.53–3.36 (m, 2H), 3.03 (ddd, 1H, $J=4.7$, 12.8 and 15.9 Hz), 2.57–2.41 (m, 1H), 2.45 (s, 3H), 2.12–1.98 (m, 1H), 1.93–1.66 (m, 2H), 1.63–1.49 (m, 1H), 1.32–1.15 (m, 1H), 1.12–0.98 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 209.4, 143.8, 143.2, 137.6, 129.5, 128.8, 127.7, 127.6, 126.9, 82.9, 76.3, 62.9, 55.3, 45.2, 43.6, 41.2, 34.5, 29.7, 26.3, 21.7.