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Unexpected products from the attempted organolithium-mediated conversion of β-methoxy aziridines into allylic amines

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Dedicated to Professor S. Florio on the occasion of his 70th birthday.

ABSTRACT

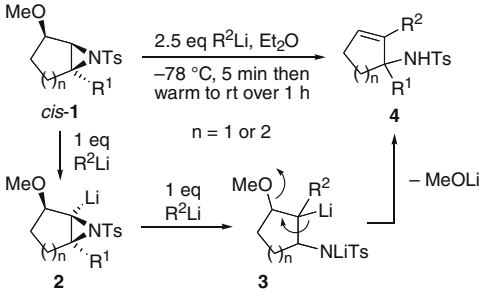
The organolithium-mediated conversion of cyclic *trans*-β-methoxy aziridines and *cis*-β-methoxy aziridines with a tertiary alkoxy group adjacent to the aziridine into the corresponding substituted allylic sulfonamides is reported. In all cases, unexpected products were observed and the reactivity was completely different from other related *cis*-β-methoxy aziridines. The product distributions are highly dependent on the organolithium reagent employed and the structure of the methoxy aziridine Thus, together with our previous reports, the full scope and limitations of this approach to allylic sulfonamides are established.

In 1996, Mioskowski and co-workers reported the direct conversion of cyclic β-methoxy epoxides into substituted allylic alcohols via reaction with organolithium reagents.[1] This pioneering contribution inspired us to develop the analogous reaction with β-methoxy *N*-sulfonyl aziridines as a route to substituted allylic sulfonamides. A generalized scheme for the process is summarized in Scheme 1.[2] Thus, treatment of aziridines *cis*-**1** ($n = 1$ or 2) with excess organolithium reagent (R^2Li) gives α-lithiated aziridines **2**. Then, carbenoid insertion of the α-lithiated aziridines **2** into the organolithium reagent (R^2Li) gives **3**[3] which can undergo methoxide elimination to ultimately form the products, allylic sulfonamides **4**.

Our efforts have included examples of reactions of aziridines derived from both cyclic[2] and acyclic alkenes[4] as well as the development of methodology for the synthesis of azaspirocyclic natural products.[5,6] Our previous work with cyclic aziridines had utilized aziridines *cis*-**1** (R^1 = H or alkyl) in reactions with a range of organolithium reagents. We had not reported any examples with *trans*-stereochemistry since the cis diastereomers are more easily prepared (aziridination of cyclic allylic alcohols gives the *cis*-hydroxy aziridines as the major or exclusive product[7]). Furthermore, we had not explored aziridines in which there was a tertiary alkoxy group adjacent to the aziridine. Thus, we decided to investigate the organolithium-mediated transformation of aziridines *trans*-**5**, *trans*-**6**, *cis*-**7** and *cis*-**8** (Fig. 1) into their corresponding substituted allylic sulfonamides. Herein, we describe some unexpected findings and hence fully map out the scope and limitations of this methodology.

Aziridines *trans*-**5**, *trans*-**6**, *cis*-**7** and *cis*-**8** were prepared by methylation (KHMDS, THF, −78 °C, Me_2SO_4 or MeI; Ag_2O, MeI, MeCN, reflux) of the corresponding known hydroxy aziridines.[7]

To start with, we investigated the reactions of β-methoxy aziridine *trans*-**5** with three different organolithium reagents (*s*-BuLi, Me_3SiCH_2Li and PhLi) (Scheme 2). The standard conditions involved reacting the aziridine with 2.5 equiv of the organolithium reagent in Et_2O at −78 °C and then allowing the solution to warm up to room temperature over 1 h before quenching with $NH_4Cl_{(aq)}$. Using *s*-BuLi and Me_3SiCH_2Li, none of the expected substituted allylic sulfonamides were produced. Instead, we isolated low yields (8–11%) of allylic sulfonamide **9**[8] (formed via β-elimination) together with 10–22% of $TsNH_2$ (which is formed via α-lithiation, carbenoid insertion into the organolithium reagent and elimination of $TsNLi_2$



Scheme 1.

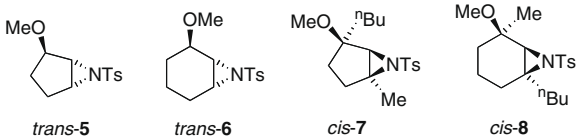


Figure 1.

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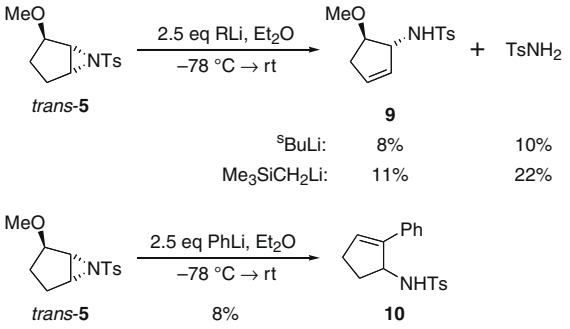


Scheme 2.

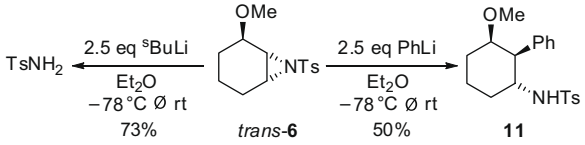
rather than methoxide). Although the yields were low, both these types of reactivities are not seen with the diastereomeric β-methoxy aziridine *cis*-**5** (which gives 33% and 67% yields of substituted allylic sulfonamides with *s*-BuLi and Me_3SiCH_2Li, respectively[2]). With PhLi, the only product isolated was the substituted allylic sulfonamide **10** (8% yield) although it was formed in considerably lower yield than β-methoxy aziridine *cis*-**5** (58% yield).[6] Disappointingly, we could not improve the yields of these reactions and we were unable to isolate the recovered starting material or any other products.

Next, the reactions between *s*-BuLi or PhLi and β-methoxy aziridine *trans*-**6** were explored but no allylic sulfonamides were formed (Scheme 3). With *s*-BuLi, a 73% yield of $TsNH_2$ was obtained, which indicates α-lithiation followed by reductive alkylation[3] without methoxide elimination. To our surprise, the reaction of PhLi with *trans*-**6** gave sulfonamide **11** (50% yield), a result of aziridine ring-opening. The regio- and stereochemistry of sulfonamide **11** are tentatively assigned based on ^1H and ^{13}C NMR spectroscopy.[9] In contrast, the diastereomeric β-methoxy aziridine *cis*-**6** was converted into the substituted allylic sulfonamides in good yields (45% using *s*-BuLi;[2] 47% using PhLi[6]).

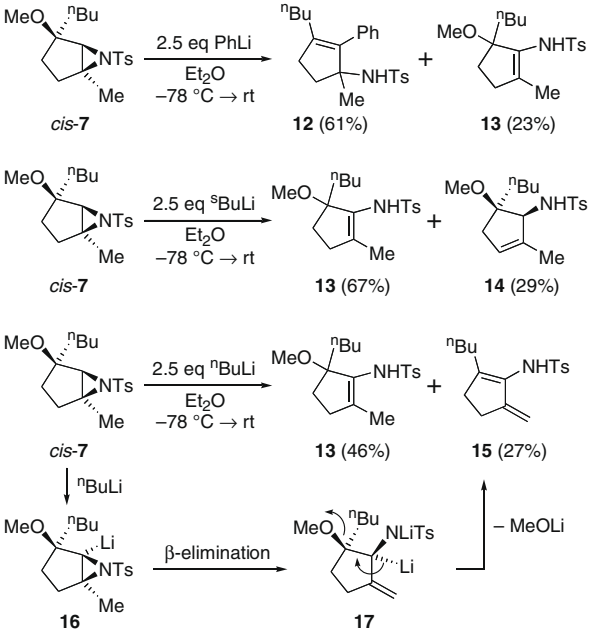
Thus, using β-methoxy aziridines *trans*-**5** and *trans*-**6** as representative examples, we conclude that a *cis*-relationship between the methoxy group and the aziridine is key to obtaining high yields of substituted allylic sulfonamides via the route outlined in Scheme 1.[10] A similar difference in reactivity for diastereomeric *syn*- and *anti*-methoxy aziridines derived from acyclic alkenes has been noted previously.[4]

Our attention then turned to β-methoxy aziridines *cis*-**7** and *cis*-**8** which contain a tertiary alkoxy substituent adjacent to the aziridine together with *cis*-disposed methoxy and aziridine groups. Encouragingly, the use of PhLi with *cis*-**7** under the standard conditions gave a 61% yield of the expected allylic sulfonamide **12**[11] (Scheme 4). This is comparable to the yield (66%) obtained by the reaction of β-methoxy aziridine with a hydrogen in place of the *n*-Bu group in *cis*-**7**.[6] In addition, enesulfonamide **13**[12] (23% yield) was isolated from the reaction and presumably forms via elimination of the α-lithiated aziridine intermediate. Such a mode of reactivity has been observed previously in cyclohexene-derived tertiary-substituted β-methoxy aziridines[5,6] but this is the first example from a cyclopentene-derived aziridine.

The reactions of β-methoxy aziridine *cis*-**7** with *s*-BuLi or *n*-BuLi gave no substituted allylic sulfonamides and enesulfonamide **13** was the major product in each case (*s*-BuLi: 67% yield; *n*-BuLi: 46% yield) (Scheme 4). However, different types of by-products were also obtained from these reactions. Use of the more basic *s*-BuLi led to allylic sulfonamide **14**[13] (29% yield), formed via a β-elimination process analogous to that which gave **9** from aziridine *trans*-**5** (see Scheme 2). With *n*-BuLi, another new type of reactivity was observed with the formation of diene sulfonamide **15**[14] (27% yield). A speculative outline mechanism for the formation of **15** is shown in Scheme 4. Thus, β-elimination of the α-lithiated aziridine intermediate **16** would lead to **17** which can undergo methoxide elimination to ultimately deliver **15** after work-up.



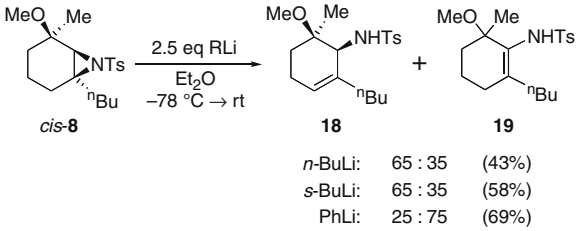
Scheme 3.



Scheme 4.

Finally, the reactions of β-methoxy aziridine *cis*-**8** were explored. No substituted allylic sulfonamides were formed with *n*-BuLi, *s*-BuLi or PhLi. Instead, mixtures of allylic sulfonamides **18** (formed by β-elimination) and enesulfonamide **19** (formed by elimination of the α-lithiated aziridine) were isolated in 43–69% yields (Scheme 5). Recrystallization of one of the mixtures of **18** and **19** gave pure enesulfonamide **19**.[15] In the lower yielding examples, starting aziridine *cis*-**8** was also recovered (20% using *n*-BuLi; 30% using *s*-BuLi).

To conclude, the reaction of β-methoxy aziridines *trans*-**5** and *trans*-**6** with organolithium reagents is not an efficient route to substituted allylic sulfonamides. The best result was obtained using PhLi and *trans*-**5** which gave an 8% yield of **10**. Instead, reactions of the corresponding *cis*-β-methoxy aziridines should be utilized as a route to the substituted allylic sulfonamides.[2,5,6] In addition, β-methoxy aziridines *cis*-**7** and *cis*-**8** which contain a tertiary alkoxy group adjacent to the aziridine do not perform particularly well in their organolithium-mediated conversion into substituted allylic sulfonamides. The expected mode of reactivity was observed in only one case: reaction of aziridine *cis*-**7** with PhLi



Scheme 5.

gave a 61% yield of allylic sulfonamide **12**. Use of other organolithium reagents and/or aziridine *cis*-**8** led to a range of different types of products: enesulfonamides **13** and **19**, alternative allylic sulfonamides **14** and **18** and dienesulfonamide **15**. Thus, with the results from β-methoxy aziridines reported in this Letter together with our previous reports,[2,4–6] we have now fully mapped out the scope and limitations of the organolithium-mediated conversion of methoxy aziridines into substituted allylic sulfonamides.

Acknowledgment

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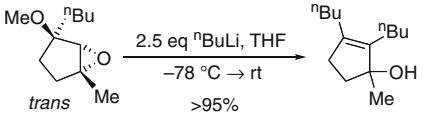
8. *Data for* **9**: colourless oil, R_f (1:1 petrol–Et_2O) 0.1; IR (Nujol mull) 3269 (NH), 1329 (SO_2), 1161 (SO_2), 1095; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, J = 8.0, 2H, *m*-C_6H_4Me), 7.33 (d, J = 8.0, 2H, *o*-C_6H_4Me), 5.84–5.81 (m, 1H,=CH), 5.34–5.31 (m, 1H, =CH), 4.47 (d, J = 9.0, 1H, NH), 4.30–4.26 (m, 1H, CHN), 3.78 (d, J = 7.0, 3.0, 1H, CHO), 3.29 (s, 3H, OMe), 2.70–2.62 (m, 1H, CH), 2.45 (s, 3H, Me), 2.26–2.20 (m, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 143.5 (*ipso*-$C_6H_4SO_2$), 137.7 (*ipso*-C_6H_4Me), 133.7 (=CH), 129.7, 128.3 (=CH), 127.2, 86.6 (CHO), 64.6 (CHN), 57.1 (OMe), 37.4 (CH_2), 21.5 (Me); MS (CI, NH_3) *m*/*z* 285 [$(M+NH_4)^+$, 100], 268 (45); HRMS (CI, NH_3) *m*/*z*: $[M+NH_4]^+$ calcd for $C_{13}H_{17}NO_3S$, 285.1267; found: 285.1268.
9. *Data for* **11**: white solid, mp 176–178 °C, R_f (1:1 petrol–Et_2O) 0.2; IR (Nujol mull) 3249 (NH), 1326 (SO_2), 1156 (SO_2), 1082; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, J = 8.0, 2H, *m*-C_6H_4Me), 7.21 (d, J = 8.0, 2H, *o*-C_6H_4Me), 7.16 (t, J = 7.5, 1.5, 1H, Ph), 7.05 (t, J = 7.5, 2H, Ph), 6.92 (d, J = 7.5, 1.5, 2H, Ph), 4.06 (d, J = 4.5, 1H, NH), 3.64 (t, J = 11.5, 4.5, 1H, CHN), 3.40 (br s, 1H, CHO), 3.02 (s, 3H, OMe), 2.48–2.44 (m, 2H, 2 × CH), 2.46 (s, 3H, Me), 2.05–1.99 (m, 1H, CH), 1.70 (app. qd, J = 13.5, 3.5, 1H, CH), 1.57–1.52 (m, 1H, CH), 1.41–1.26 (m, 2H, 2 × CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 142.9 (*ipso*-$C_6H_4SO_2$), 139.1 (*ipso*-C_6H_4Me), 136.9 (*ipso*-Ph), 129.4, 129.0, 128.2, 127.2, 126.8, 80.0 (CHO), 56.8 (OMe), 54.1 (CH), 51.8 (CH), 34.7 (CH_2), 28.1 (CH_2), 21.5 (Me), 18.7 (CH_2); MS (CI, NH_3) *m*/*z* 377 [$(M+NH_4)^+$, 40], 360 (100); HRMS (CI, NH_3) *m*/*z*: $[M+H]^+$ calcd for $C_{20}H_{25}NO_3S$, 360.1628; found: 360.1626.
10. In Mioskowski's original report (see Ref. 1), there was one example of the conversion of a *trans*-β-methoxy epoxide into a substituted allylic alcohol (>95% yield):



11. *Data for* **12**: colourless oil, R_f (4:1 hexane–EtOAc) 0.5; IR (film) 3265 (NH), 2956, 1452, 1325 (SO_2), 1154 (SO_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, J = 8.0, 2H, *m*-C_6H_4Me), 7.61 (d, J = 7.5, 1.0, 1H, Ph), 7.46 (t, J = 7.5, 2H, Ph), 7.39–7.10 (m, 4H, 4 × CH), 4.58–4.54 (m, 1H, NH), 2.48–2.28 (m, 3H, 3 × CH), 2.40 (s, 3H, Me), 1.99–1.89 (m, 3H, 3 × CH), 1.33 (app. quintet, J = 7.5, 2H, CH_2), 1.28 (s, 3H, Me), 1.21 (app. sextet, J = 7.5, 2H, CH_2), 0.82 (t, J = 7.5, 3H, Me); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 143.9 (C), 142.7 (C), 140.7 (C), 140.3 (C), 135.5 (C), 129.6 (CH) 129.4 (CH), 128.1 (CH), 127.1 (CH), 126.8 (CH), 71.2 (CN), 37.9 (CH_2), 32.3 (CH_2), 30.0 (CH_2), 29.1 (CH_2), 25.3 (Me), 22.5 (CH_2), 21.5 (Me), 13.9 (Me); MS (ESI) *m*/*z* 406 [$(M+Na)^+$, 35], 260 (40), 213 (100); HRMS (ESI) *m*/*z*: $[M+Na]^+$ calcd for $C_{23}H_{29}NO_2S$, 406.1822; found: 406.1807.
12. *Data for* **13**: colourless oil, R_f (4:1 hexane–EtOAc) 0.2; IR (film) 3252 (NH), 2931, 1460, 1383, 1323 (SO_2), 1160 (SO_2), 1092; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, J = 8.0, 2H, *m*-C_6H_4Me), 7.28 (d, J = 8.0, 2H, *o*-C_6H_4Me), 5.66 (br s, 1H, NH), 2.95 (s, 3H, OMe), 2.41 (s, 3H, Me), 2.25–2.22 (m, 2H, 2 × CH), 1.89–1.72 (m, 2H, 2 × CH), 1.84 (s, 3H, Me), 1.19–0.94 (m, 5H, 5 × CH), 0.82–0.77 (m, 1H, CH), 0.77 (t, J = 7.0, 3H, Me); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 143.4 (*ipso*-$C_6H_4SO_2$), 138.4 (C), 136.3 (C), 129.4 (*m*-C_6H_4Me), 128.3 (=C), 127.2 (*o*-C_6H_4Me), 90.4 (CO), 49.7 (OMe), 37.5 (CH_2), 33.9 (CH_2), 27.5 (CH_2), 25.5 (CH_2), 23.0 (CH_2), 21.5 (Me), 15.2 (Me), 13.9 (Me); MS (ESI) *m*/*z* 360 [$(M+Na)^+$, 20], 344 (20), 338 (15), 328 (25), 322 (50), 306 (100); HRMS (ESI) *m*/*z*: $[M+H]^+$ calcd for $C_{18}H_{27}NO_3S$, 338.1790; found: 338.1784.
13. *Data for* **14**: colourless oil, R_f (99:1 CH_2Cl_2–acetone) 0.3; IR (film) 3306 (NH), 2933, 1587 (C=C), 1456, 1337 (SO_2), 1161 (SO_2), 1091; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 8.0, 2H, *m*-C_6H_4Me), 7.29 (d, J = 8.0, 2H, *o*-C_6H_4Me), 5.39 (br d, J = 7.0, 1H, NH), 5.31 (app. quin, J = 1.5, 1H, =CH), 3.87 (br d, J = 7.0, 1H, CHN), 3.11 (s, 3H, OMe), 2.42 (s, 3H, Me), 2.40–2.35 (m, 1H, CH), 2.15–2.10 (m, 1H, CH), 1.70 (br s, 3H, Me), 1.25–0.88 (m, 6H, 6 × CH), 0.75 (t, J = 7.0, 3H, Me); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 143.1 (*ipso*-$C_6H_4SO_2$), 139.9 (=C), 138.2 (*ipso*-C_6H_4Me), 129.5 (*m*-C_6H_4Me), 127.4 (*o*-C_6H_4Me), 123.2 (=CH), 84.3 (CO), 65.2 (OMe), 51.0 (CHN), 37.3 (CH_2), 35.1 (CH_2), 26.2 (CH_2), 23.0 (CH_2), 21.5 (Me), 14.3 (Me), 13.8 (Me); MS (ESI) *m*/*z* 360 [$(M+Na)^+$, 75], 338 (40), 306 (30), 167 (100); HRMS (ESI) *m*/*z*: $[M+Na]^+$ calcd for $C_{18}H_{27}NO_3S$, 360.1604; found: 360.1605.
14. *Data for* **15**: colourless oil, R_f (9:1 hexane–EtOAc) 0.3; IR (film) 3259 (NH), 2956, 2928, 1383, 1327 (SO_2), 1164 (SO_2), 1093; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, J = 8.0, 2H, *m*-C_6H_4Me), 7.25 (d, J = 8.0, 2H, *o*-C_6H_4Me), 5.50 (br s, 1H, NH), 4.47 (br s, 1H, $=CH_AH_B$), 4.37 (t, J = 2.5, 1H, $=CH_AH_B$), 2.49–2.36 (m, 4H, 4 × CH), 2.42 (s, 3H, Me), 2.16–2.13 (m, 2H, 2 × CH), 1.32–1.19 (m, 4H, 4 × CH), 0.87 (t, J = 7.5, 3H, Me); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 151.6 (=C), 150.3 (=C), 143.5 (*ipso*-$C_6H_4SO_2$), 137.5 (*ipso*-C_6H_4Me), 130.7 (=C), 129.4 (*m*-C_6H_4Me), 127.3 (*o*-C_6H_4Me), 99.2 ($=CH_2$), 30.7 (CH_2), 29.4 (CH_2), 28.8 (CH_2), 27.3 (CH_2), 22.8 (CH_2), 21.5 (Me), 13.9 (Me); MS (ESI) *m*/*z* 328 [$(M+Na)^+$, 40], 322 (35), 306 (100); HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{17}H_{23}NO_2S$, 306.1522; found: 306.1519.
15. *Data for* **19**: white solid, R_f (1:1 hexane–Et_2O) 0.2; IR (Nujol mull) 3377 (NH), 1341 (SO_2), 1160 (SO_2), 1092; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 8.0, 2H, *m*-C_6H_4Me), 7.29 (d, J = 8.0, 2H, *o*-C_6H_4Me), 5.93 (s, 1H, NH), 3.08 (s, 3H, OMe), 2.40 (s, 3H, Me), 2.08–2.00 (m, 3H, 3 × CH), 1.90–1.62 (m, 3H, 3 × CH), 1.54–1.48 (m, 1H, CH), 1.32–1.18 (m, 3H, 3 × CH), 1.24 (s, 3H, Me), 1.05–0.89 (m, 2H, 2 × CH), 0.74 (t, J = 7.5, 3H, Me); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 142.9 (*ipso*-$C_6H_4SO_2$), 139.4 (C), 137.5 (C), 129.2 (*m*-C_6H_4Me), 128.4 (=C), 126.7 (*o*-C_6H_4Me), 77.2 (CO), 49.3 (OMe), 33.4 (CH_2), 32.5 (CH_2), 30.9 (Me), 29.4 (CH_2), 29.1 (CH_2), 24.2 (Me), 22.5 (CH_2), 21.5 (Me), 19.5 (CH_2), 13.8 (Me); MS (ESI) *m*/*z* 374 [$(M+Na)^+$, 100], 358 (20), 318 (20), 226 (20), 181 (50), 165 (40); HRMS (ESI) *m*/*z*: $[M+Na]^+$ calcd for $C_{19}H_{29}NO_3S$, 374.1941; found: 374.1932. Diagnostic signals for **18**: ^{1}H NMR (400 MHz, $CDCl_3$) 5.47–5.44 (m, 1H, =CH), 4.89 (d, J = 9.0, 1H, NH), 3.88 (br d, J = 9.0, 1H, CHN), 3.12 (s, 3H, OMe), 2.41 (s, 3H, Me), 1.18 (s, 3H, Me), 0.77 (t, J = 7.5, 3H, Me).