Titanium-Mediated Cyclopropanation on Diesters: Mechanistic Study on the Dramatic Effects of Selected Parameters

Mouhamad Jida, Xavier Gaucher, Jean Ollivier*

Laboratoire de Synthèse Organique et Méthodologie, UMR 8182, Institut de Chimie Moléculaire et des Matériaux d'Orsay, Université de Paris-Sud XI, 91405 Orsay, France
Fax +33(1)69157252; E-mail: jean.ollivier@u-psud.fr

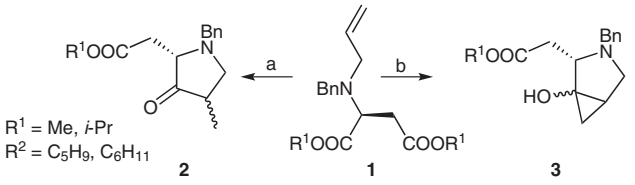
Received 5 April 2010

Dedicated to Professor Henri Kagan on the occasion of his 80th birthday

Abstract: Competitive reactions of diisopropyloxy(η^2-alkene)titanium on *N*-allyl diesters derived from natural amino acids and performed under varying conditions (temperature, nature, and concentration of Grignard reagents) show different regio- and chemoselectivities. In light of the isolated reaction products, a possible mechanism of the formation of original products is discussed.

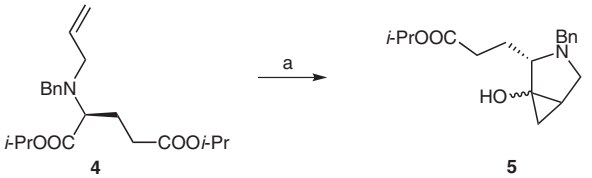
Key words: esters, fused ring systems, heterocycles, regioselectivity, titanium, Kulninkovich reaction

Recently,[1] we have studied the regio- and stereoselectivity of the Kulinkovich reaction[2] performed on aspartic acid derivative **1**, and we observed, under classical experimental conditions [Ti(O*i*-Pr)$_4$, $C_6H_{11}MgCl$], the formation of only the unexpected pyrrolidinone **2**. On the other hand, Joullié et al.[3] obtained the expected azabicyclo[3.1.0]hexan-1-ol **3** when performing the same reaction, but with ClTi(O*i*-Pr)$_3$ as catalyst (Scheme 1).



Scheme 1 *Reagents and conditions*: (a) R^2MgBr, Ti(O*i*-Pr)$_4$, Et_2O–THF, 20 °C; (b) R^2MgBr, ClTi(O*i*-Pr)$_3$, Et_2O, THF, 20 °C.

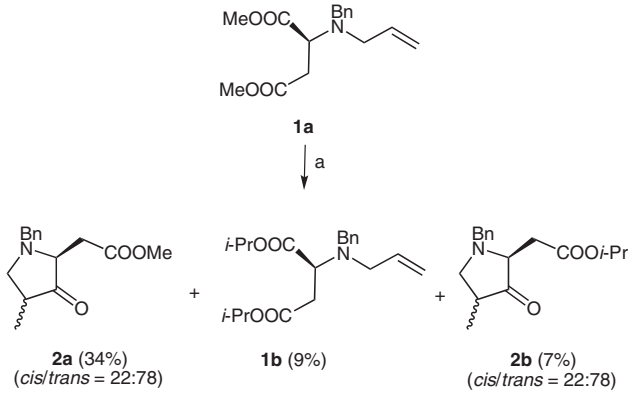
It is noteworthy that the same reaction, performed on the homologous glutamic acid derivative **4**, only afforded the corresponding azabicyclo[3.1.0]hexan-1-ol **5** even in the presence of the titanium tetraisopropoxide (Scheme 2).[4]



Scheme 2 *Reagents and conditions*: (a) $C_6H_{11}MgCl$, Ti(O*i*-Pr)$_4$, Et_2O–THF, 20 °C.

SYNLETT 2010, No. 11, pp 1627–1630
Advanced online publication: 01.06.2010
DOI: 10.1055/s-0029-1220125; Art ID: D08410ST

In the present work, we observed that, under classical cyclopropanation conditions [1 equiv of Ti(O*i*-Pr)$_4$, 4–5 equiv of $C_6H_{11}MgCl$ (2–2.4 M in Et_2O), Et_2O–THF (1:1), 4 h, 20 °C], the *N*-allyl dimethyl aspartate derivative **1a** afforded an inseparable mixture of pyrrolidinones **2a**,**b** and a small amount of *trans*-esterified aspartate derivative **1b**. Moreover, from the diesters **1a** or **1b**, no product resulting from a possible reaction between the excess of Grignard and the ester or ketone functions of the newly formed pyrrolidinones **2a** or **2b** was observed (Scheme 3).



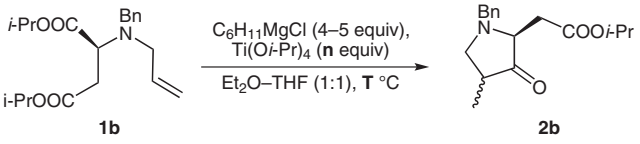
Scheme 3 *Reagents and conditions*: (a) $C_6H_{11}MgCl$, Ti(O*i*-Pr)$_4$, Et_2O–THF, 20 °C.

To avoid *trans*-esterification, all the reactions were thus performed on isopropyl esters **1b**. The reactions were carried out in presence of titanium catalyst by dropwise addition of four equivalents of cyclohexyl Grignard reagent at a given temperature over three hours. Then, after an additional hour at the same temperature, the reaction was quenched and the products isolated. NMR analysis of the crude product allowed the determination of the *cis*/*trans* ratios, while yields were calculated after purification by column chromatography.

Parameters such as temperature and amount of titanium isopropylate, which are able to affect the sequence of the reaction, were tested (Table 1).

Firstly, we noted that the use of either 5 or 6 equivalents of the Grignard reagent had no significant influence on the yield or *cis*/*trans* product ratio of the reaction. Unsatisfactory yields were observed for the reactions carried out at low temperatures (entries 1–3) while the best result was

Table 1 Effects of the Amount of Ti(O*i*-Pr)$_4$ and the Temperature on the Formation of Pyrrolidinone **2b**



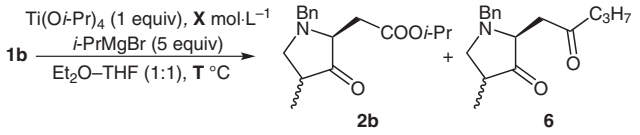
1b **2b**

Entry	Ti(O*i*-Pr)$_4$·(n)	Temp (°C)	Yield (%)	Ratio (*cis*/*trans*)
1	1	–78	18	27:73
2	1	–40	25	27:73
3	1	0	34	24:76
4	1	20	53	20:80
5	1	50	45	18:82
6	0.1	20	20	22:78
7	2	20	35	23:77

obtained performing the reaction at room temperature (entry 4). At a higher temperature of 50 °C (entry 5) the yield was lower, but the selectivity was essentially maintained. However, reducing (entry 6) or increasing (entry 7) the amounts of the titanium species led to lower yields although the variations of the *cis*/*trans* ratios remained almost unchanged.

On the other hand, isopropyl magnesium bromide or chloride had been initially used by Sato[5] as a source of Grignard reagent in certain intramolecular cyclopropanation reactions; surprisingly, when applied to the aspartate derivative **1b**, the formation of the pyrrolidinone **6** was observed, and in yields highly dependent upon the concentration of the organometallic reagent (Table 2).

Table 2 Effects of the Concentration of Grignard Reagent on the Synthesis of Pyrrolidinones **2b** and **6**

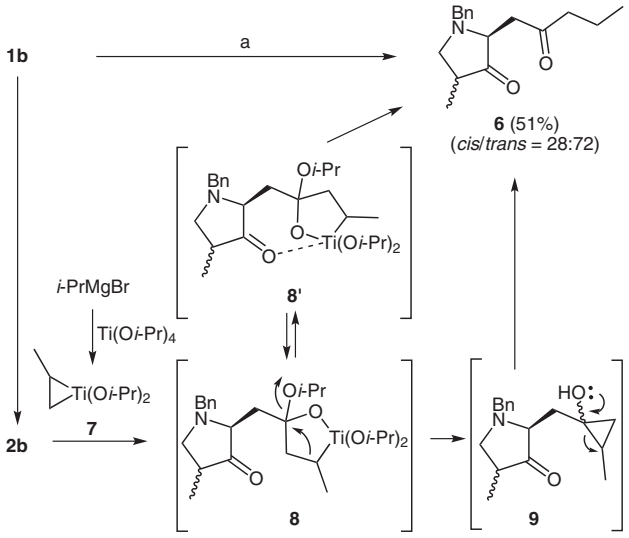


2b **6**

Entry	*i*-PrMgBr (mol·L^{-1})	Temp (°C)	Yield of **2b** (%), ratio (*cis*/*trans*)	Yield of **6** (%), ratio (*cis*/*trans*)
1	0.5	20	49 (19:81)	0
2	1.2	20	28 (22:78)	16 (21:79)
3	1.8	20	15 (24:76)	29 (26:74)
4	2.4	20	0	51 (28:72)
5	2.4	0	0	27 (25:75)
6	2.4	–40	0	23 (27:73)
7	2.4	–78	0	13 (23:77)

Indeed, in the presence of five equivalents of isopropyl magnesium bromide at a concentration of approximately 0.5 mol L^{-1} (entry 1), the aspartate derivative only furnished pyrrolidinones **2b** with a yield close to that previously obtained with cyclohexyl magnesium chloride and similar diastereomeric ratio. However, at concentrations above 1 mol L^{-1} at room temperature, a dramatic effect was observed, and the formation of ketone **6** became preponderant to exclusive, according to the increasing concentration (entries 2–4). On the other hand, lowering the temperature only affected the yield of the product negatively (entry 5–7).

Although high concentrations promote intermolecular reactions, no report of such selectivity in the Kulinkovich reaction has appeared in the literature.[6] As depicted in Scheme 4, the formation of the ketone **6** can occur through the incorporation of titanium complex **7** in the ester function of the pyrrolidinone **2b** giving the oxatitanacyclopentane **8**, then the cyclopropanol **9** which, on ring opening, leads to the ketopyrrolidinone **6**[7] (Scheme 4).



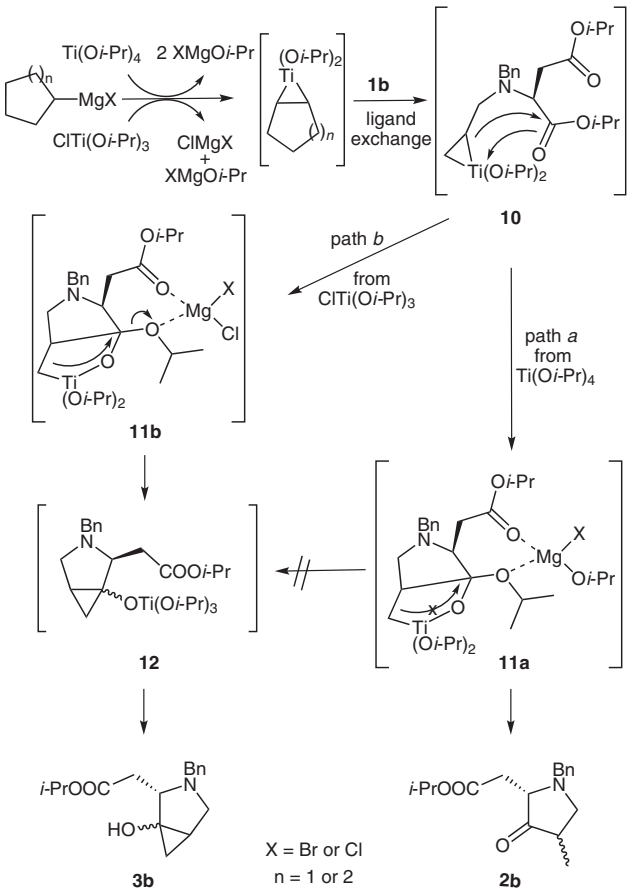
Scheme 4 *Reagents and conditions*: (a) Ti(O*i*-Pr)$_4$ (1 equiv), 2.4 M *i*-PrMgBr (5 equiv), Et$_2$O–THF (1:1), 20 °C.

Compared to the bulky cyclopentyl- or cyclohexylmagnesium halide, the incorporation of the titanium complex **7** seems quite conceivable. The hypothesis of a possible coordination between the titanium species and the oxygen of the ketone function could stabilize the complex form **8′** sufficiently, such that simple hydrolysis would lead directly to the ketopyrrolidinone **6**. On the other hand, the ring opening on the side chain could be possible but perhaps less likely.

This result can be extended to the formation of the monocyclic pyrrolidinone skeleton of ester **2b** (vide supra Scheme 1). Indeed, as represented in Scheme 5, following formation of titanium species **10**, the coordination of the weak Lewis acid (XMgO*i*-Pr) from Ti(O*i*-Pr)$_4$ between the ester on the side chain and the O*i*-Pr residue of the oxatitanacyclopentane **11a** (path a) does not constitute a sufficient driving force to achieve the contraction cycle, thus a subsequent hydrolysis leads to the pyrrolidinone

2b. In support of this theory, performing the reaction in the presence of trimethylsilyl chloride gives a similar result. On the other hand, the reaction carried out with $ClTi(O\textit{i}\text{-}Pr)_3$ (path b) releases a stronger Lewis acid (XMgCl) which, on coordination to give the complex **11b**, is capable of inducing formation of the titanium salt **12**. In this case, simple hydrolysis yields the stable azabicyclo[3.1.0]hexanol **3b** isolated by Joullié.

Further evidence supporting our previous assumption came to light when extending this experiment to the glutamate derivative **4** which, as we had reported before, does not undergo cyclopropyl ring opening under titanium isopropoxide mediated conditions (vide supra Scheme 2).

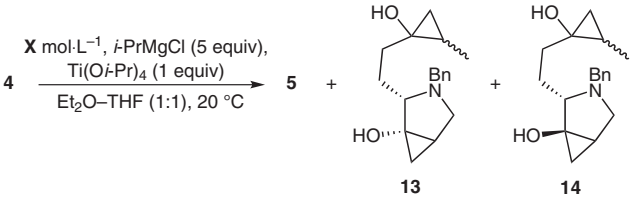


Scheme 5 *Reagents and conditions*: $Ti(O\textit{i}\text{-}Pr)_4$ or $ClTi(O\textit{i}\text{-}Pr)_3$, C_5H_9MgBr or $C_6H_{11}MgCl$, Et_2O–THF, 20 °C.

Indeed, extending the ester on the side chain does not allow the previous coordination and, as expected, a *cis*/*trans* inseparable mixture of azabicyclo[3.1.0]hexanols **13** and **14** resulting from a double Kulinkovich reaction occurred in the presence of a high concentration of Grignard reagent (Table 3).

In conclusion, we have investigated alternative experimental conditions allowing different cyclopropanol derivatives to be obtained. The influence of several parameters such as temperature, titanium catalyst, nature, and concentration of Grignard reagent were studied in order to optimize reactions which may even be competitive.

Table 3 Effects of the Concentration of Grignard Reagent on the Synthesis of Cyclopropanols **5**, **13**, and **14**[7]



Entry	*i*-PrMgBr (X mol·L^{-1})	Yield of **5** (%), ratio (*cis*/*trans*)	Yield of **13** (%), ratio (*cis*/*trans*)	Yield of **14** (%), ratio (*cis*/*trans*)
1	0.5	50 (69:31)	0	0
2	2.4	0	26 (60:40)	17 (64:36)

Meanwhile, novel mechanisms have been proposed to explain the formation of primary or secondary unexpected products.

Acknowledgment

The authors gratefully acknowledge Professor Oleg Kulinkovich, Belarusian State University of Minsk, for helpful discussions.

References and Notes

(1) Garnier, J.-M.; Jida, M.; Ollivier, J. *Synlett* **2006**, 2739.
(2) Kulinkovich, O. G. *Chem. Rev.* **2003**, *103*, 2597.
(3) Faler, C. A.; Joullié, M. M. *Tetrahedron Lett.* **2008**, *49*, 6512.
(4) Jida, M. *PhD Thesis*; Université de Paris-Sud 11: France, **2008**.
(5) (a) Kasatkin, A.; Nakagawa, T.; Okamoto, S.; Sato, F. *J. Am. Chem. Soc.* **1995**, *117*, 3881. (b) Nakagawa, T.; Kasatkin, A.; Sato, F. *Tetrahedron Lett.* **1995**, *36*, 3207. (c) Harada, K.; Urabe, H.; Sato, F. *Tetrahedron Lett.* **1995**, *36*, 3203. (d) Urabe, H.; Hata, T.; Sato, F. *Tetrahedron Lett.* **1995**, *36*, 4261.
(6) Kulinkovich, O. G.; Kananovich, D. G. *Eur. J. Org. Chem.* **2007**, 2121.
(7) Selected Data
***tert*-Butyl 3-{3-Benzyl-1-hydroxy-3-azabicyclo-[3.1.0]hex-2-yl} Propanoate (5)**
Colourless liquid. IR (neat): 3333, 3027, 2931, 1740, 1602 cm^{-1}. ^{1}H NMR (360 MHz, $CDCl_3$): δ = 7.34–7.24 (m, 10 H, *cis* + *trans*), 5.18–5.01 (m, 2 H, *cis* + *trans*), 4.09 (d, *J* = 13.7 Hz, 1 H, *cis*), 4.00 (d, *J* = 13.3 Hz, 1 H, *trans*), 3.86 (d, *J* = 13.7 Hz, 1 H, *cis*), 3.75 (d, *J* = 13.3 Hz, 1 H, *trans*), 3.23 (dd, *J* = 12.6, 6.1 Hz, 1 H, *cis*), 3.15 (dd, *J* = 9.7, 4.7 Hz, 1 H, *trans*), 2.80 (t, *J* = 4.5 Hz, 1 H, *trans*), 2.69 (t, *J* = 4.5 Hz, 1 H, *cis*), 2.55 (d, *J* = 12.6 Hz, 1 H, *cis*), 2.36 (d, *J* = 9.7 Hz, 1 H, *trans*), 2.06–1.90 (m, 4 H, *cis* + *trans*), 1.87–1.73 (m, 4 H, *cis* + *trans*), 1.60–1.54 (m, 2 H, *cis* + *trans*), 1.28–1.23 (m, 2 H, *cis* + *trans*), 1.25 (d, *J* = 6.2 Hz, 3 H, *trans*), 1.22 (d, *J* = 6.9 Hz, 3 H, *cis*), 1.20 (d, *J* = 6.9 Hz, 3 H, *cis*), 1.18 (t, *J* = 4.8 Hz, 1 H, *trans*), 1.15 (d, *J* = 6.2 Hz, 3 H, *trans*), 1.11 (dd, *J* = 9.0, 5.8 Hz, 1 H, *cis*), 0.87 (dd, *J* = 10.1, 4.8 Hz, 1 H, *trans*), 0.46 (t, *J* = 5.8 Hz, 1 H, *cis*). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 170.8 (*cis*), 170.6 (*trans*), 137.9 (*cis*), 137.8 (*trans*), 128.9 (*cis*), 128.7 (*trans*), 128.5 (*cis*), 128.3 (*trans*), 127.3 (*cis*), 127.2 (*trans*), 68.4 (*cis*), 68.2 (*trans*), 66.6 (*cis*), 65.8(*trans*), 59.4 (*cis*), 59.1 (*trans*), 58.3 (*cis*), 58.1 (*trans*),

55.7 (*trans*), 54.9 (*cis*), 36.8 (*cis*), 35.9 (*trans*), 25.8 (*cis*), 24.5 (*trans*), 21.7 (*cis*), 21.1 (*trans*), 20.9 (*cis*), 20.2 (*trans*), 15.8 (*cis*), 15.6 (*trans*). MS (EI, *trans* isomer): *m/z* (%) = 303(9) [M$^+$], 160 (48), 96 (27), 91 (100). MS (EI, *cis* isomer): *m/z* (%) = 303(6) [M$^+$], 234 (45), 188 (42), 91 (100). HRMS (ES): *m/z* calcd for $C_{18}H_{26}NO_3$ [M + H]$^+$: 304.19070; found: 304.19057.

1-Benzyl-4-methyl-2-(2-oxopentyl)-3-pyrrolidinone (6)

Colourless liquid. IR (neat): 3057, 3027, 2955, 1758, 1603 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.36–7.27 (m, 10 H, *cis* + *trans*), 3.88 (d, *J* = 13.0 Hz, 1 H, *cis*), 3.85 (d, *J* = 13.0 Hz, 1 H, *trans*), 3.48 (d, *J* = 13.7 Hz, 1 H, *cis*), 3.46 (d, *J* = 13.0 Hz, 1 H, *trans*), 3.40 (t, *J* = 8.3 Hz, 1 H, *trans*), 3.29 (t, *J* = 5.0 Hz, 1 H, *cis*), 3.01 (dd, *J* = 11.2, 9.0 Hz, 1 H, *trans*), 2.85 (dd, *J* = 12.6, 7.2 Hz, 1 H, *cis*), 2.73 (dd, *J* = 12.6, 7.2 Hz, 1 H, *cis*), 2.68 (dd, *J* = 11.2, 8.3 Hz, 2 H, *cis*), 2.67–2.60 (m, 2 H, *cis* + *trans*), 2.63 (dd, *J* = 10.0, 5.0 Hz, 2 H, *trans*), 2.27–2.20 (m, 4 H, *cis* + *trans*), 2.08 (dd, *J* = 11.2, 9.0 Hz, 1 H, *trans*), 1.60–1.54 (m, 4 H, *cis* + *trans*), 1.21 (d, *J* = 7.6 Hz, 3 H, *cis*), 1.14 (d, *J* = 7.2 Hz, 3 H, *trans*), 1.07 (t, *J* = 7.6 Hz, 3 H, *cis*), 1.06 (t, *J* = 7.6 Hz, 3 H, *trans*). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 217.7 (*cis*), 217.5 (*trans*), 208.1 (*cis*), 207.8 (*trans*), 138.2 (*cis*), 138.0 (*trans*), 128.9 (*trans*), 128.7 (*cis*), 128.4 (*cis*), 128.2 (*trans*), 127.5 (*trans*), 127.3 (*cis*), 66.4 (*trans*), 66.0 (*cis*), 59.4 (*trans*), 58.9 (*cis*), 57.9 (*trans*), 56.7 (*cis*), 45.2 (*cis*), 43.1 (*trans*), 41.9 (*cis* + *trans*), 36.2 (*cis*), 35.3 (*trans*), 18.0 (*cis*), 17.1 (*cis*), 17.0 (*trans*), 16.0 (*cis*), 13.7 (*trans*), 11.9 (*trans*). MS (EI, *trans* isomer): *m/z* (%) = 273 (5) [M$^+$], 86 (40), 84 (61), 55 (55), 51 (35), 49 (100), 44 (49), 40 (90). MS (EI, *cis* isomer): *m/z* (%) = 273 (4) [M$^+$], 91 (100), 86 (41). HRMS (ES): *m/z* calcd for $C_{17}H_{24}NO_2$ [M + H]$^+$: 274.18020; found: 274.18082.

(1*S*,2*S*)-3-Benzyl-2-[2-(1-hydroxy-2-methylcyclopropyl)-ethyl]-3-azabicyclo[3.1.0]hexan-1-ol (13)

[Insepable mixture of undetermined *cis* and *trans* diastereomers (ratio 60:40: major *a* and minor *b*) on the side chain.]

Colorless liquid. IR (neat): 3030, 2929, 2797, 1603 cm^{-1}. ^{1}H NMR (360 MHz, $CDCl_3$): δ = 7.34–7.26 (m, 10 H, *a* + *b*), 4.14 (d, *J* = 14.4 Hz, 1 H, *b*), 4.08 (d, *J* = 14.4 Hz, 1 H, *b*), 3.76 (d, *J* = 13.7 Hz, 1 H, *a*), 3.71 (d, *J* = 13.7 Hz, 1 H, *a*), 3.23 (dd, *J* = 12.6, 5.8 Hz, 1 H, *b*), 3.06 (dd, *J* = 9.7, 4.3 Hz, 1 H, *a*), 2.92 (t, *J* = 4.7 Hz, 1 H, *a*), 2.65 (t, *J* = 4.2 Hz, 1 H, *b*), 2.53 (d, *J* = 12.6 Hz, 1 H, *b*), 2.44 (d, *J* = 9.7 Hz, 1 H, *a*), 2.21–2.17 (m, 4 H, *a* + *b*), 2.06–1.97 (m, 4 H, *a* + *b*), 1.63–1.54 (m, 2 H, *a* + *b*), 1.44–1.39 (m, 2 H, *a* + *b*), 1.40 (t, *J* = 5.1 Hz, 1 H, *a*), 1.30–1.24 (m, 2 H, *a* + *b*), 1.26 (t, *J* = 5.8 Hz, 1 H, *b*), 1.18–1.08 (m, 2 H, *a* + *b*), 1.16 (d, *J* = 6.2 Hz, 3 H, *a*), 1.07 (d, *J* = 6.2 Hz, 3 H, *b*), 0.97–0.87 (m, 4 H, *a* + *b*), 0.81 (dd, *J* = 9.4, 5.1 Hz, 1 H, *a*), 0.07 (dd, *J* = 10.2, 5.8 Hz, 1 H, *b*). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 139.7 (*b*), 137.9 (*a*), 129.6 (*b*), 128,7 (*a*), 128.5 (*b*), 128.3 (*a*), 128.2 (*b*), 127.5 (*a*), 70.2 (*b*), 70.1 (*a*), 65.7 (*a*), 64.6 (*b*), 57.8 (*b*), 57.7 (*a*), 55.8 (*a*), 55.7 (*b*), 54.1 (*a*), 53.4 (*b*), 37.3 (*a*), 31.1 (*b*), 24.6 (*a*), 24.5 (*b*), 22.7 (*a*), 22.1 (*b*), 20.2 (*a*), 18.4 (*b*), 17.4 (*a*), 16.5 (*b*), 14.4 (*a*), 13.8 (*b*), 12.4 (*b*), 11.4 (*a*). MS (EI, isomer *a*): *m/z* (%) = 287 (5)[M$^+$], 218 (18), 200(20), 188(47), 91(100). MS (EI, isomer *b*): *m/z* (%) = 287 (6) [M$^+$], 218 (17), 200(26), 188 (29), 91(100). HRMS (ES): *m/z* calcd for $C_{18}H_{26}NO_2$ [M + H]$^+$: 288.19580; found: 288.19622.

(1*R*,2*S*)-3-Benzyl-2-[2-(1-hydroxy-2-methylcyclopropyl)ethyl]-3-azabicyclo[3.1.0]hexan-1-ol (14)

[Inseparable mixture of undetermined *cis* and *trans* diastereomers (ratio 64:36: major *a* and minor *b*) on the side chain.]

Colourless liquid. IR (neat): 3036, 2929, 2791, 1602 cm^{-1}. ^{1}H NMR (360 MHz, $CDCl_3$): δ = 7.34–7.25 (m, 10 H, *a* + *b*), 3.84 (d, *J* = 13.3 Hz, 1 H, *a*), 3.83 (d, *J* = 13.3 Hz, 1 H, *b*), 3.64 (d, *J* = 13.3 Hz, 1 H, *a*), 3.63 (d, *J* = 13.3 Hz, 1 H, *b*), 3.17 (dd, *J* = 10.1, 4.7 Hz, 1 H, *b*), 3.02 (t, *J* = 4.2 Hz, 1 H, *a*), 2.97 (t, *J* = 4.2 Hz, 1 H, *b*), 2.34 (d, *J* = 9.4 Hz, 1 H, *a*), 2.31 (d, *J* = 10.1 Hz, 1 H, *b*), 2.29 (dd, *J* = 9.4, 4.0 Hz, 1 H, *a*), 2.01–1.92 (m, 4 H, *a* + *b*), 1.83–1.73 (m, 4 H, *a* + *b*), 1.59–1.54 (m, 2 H, *a* + *b*), 1.47–1.45 (m, 2 H, *a* + *b*), 1.29 (t, *J* = 6.7 Hz, 1 H, *a*), 1.28–1.25 (m, 2 H, *a* + *b*), 1.17 (dd, *J* = 9.0, 5.4 Hz, 1 H, *b*), 1.06 (d, *J* = 6.7 Hz, 3 H, *a*), 1.04 (d, *J* = 6.7 Hz, 3 H, *b*), 0.93 (dd, *J* = 9.0, 6.7 Hz, 1 H, *a*), 0.86–0.81 (m, 2 H, *a* + *b*), 0.76–0.73 (m, 4 H, *a* + *b*), 0.02 (t, *J* = 10.2 Hz, 1 H, *b*). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 139.2 (*b*), 137.6 (*a*), 129.4 (*a* + *b*), 128,7 (*b*), 128.6 (*a*), 128.3 (*b*), 127.1 (*a*), 67.1 (*b*), 66.3 (*a*), 63.4 (*a*), 63.2 (*b*), 58.7 (*a*), 58.4 (*b*), 57.8 (*a*), 57.4 (*b*), 54.7 (*b*), 54.2 (*a*), 30.8 (*a*), 30.4 (*b*), 24.6 (*a*), 24.4 (*b*), 21.6 (*a*), 20.4 (*b*), 20.2 (*a*), 20.0 (*b*), 19.6 (*a*), 19.1 (*b*), 15.0 (*a*), 14.9 (*b*), 14.6 (*b*), 14.3 (*a*). MS (EI, isomer *a*): *m/z* (%) = 287 (9)[M$^+$], 218 (21), 200 (23), 188 (22), 91 (100). MS (EI, isomer *b*): *m/z* (%) = 287(6) [M$^+$], 218 (28), 200 (19), 188 (33), 91 (100). HRMS (ES): *m/z* calcd for $C_{18}H_{26}NO_2$ [M + H]$^+$: 288.19580; found: 288.19653.