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New electronically enriched boronobutadienes for the synthesis of hydroxylated cyclohexenes via tandem [4+2]/allylboration

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Abstract—This communication describes the preparation and behavior of ether-substituted 1-boronobutadienes **1** and **2** in the Vaultier tandem [4+2]/allylboration three-component reaction involving electron-poor dienophiles and aldehydes. Whereas diene **1** failed to undergo the second, allylboration step of this process, diene **2** reacted with maleimides to give products **12**, and even reacted with moderately activated dienophiles such as acrylates and acrylamide derivative **14** to provide a new stereoselective approach to the synthesis of hydroxyalkylated cyclohexene derivatives.

Our laboratory has developed a longstanding interest in the design of multicomponent reactions based on the powerful [4+2]/allylboration tandem reaction strategy.[1] Vaultier and co-workers were first to demonstrate the value of simple 1-boronobutadienes as substrates in Diels–Alder cycloadditions.[2] As shown in generic fashion in Figure 1, these versatile dienes react with activated dienophiles to give the usual [4+2] cycloadducts. This transformation constitutes the first step in the tandem process, and sets up a reactive allylboronate unit crucial for the second step. In the latter, [4+2] cycloadduct undergoes an allylboration with an aldehyde component to provide the final hydroxyalkyl-substituted cyclohexene product with high stereoselectivity.

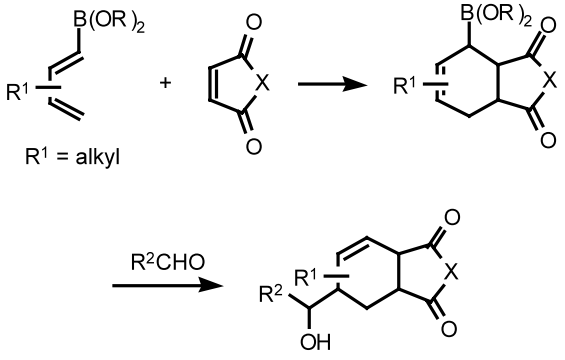
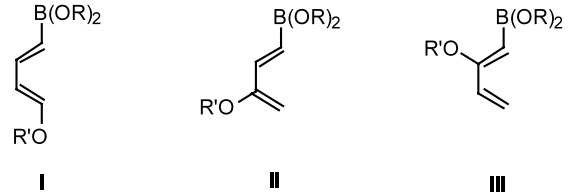


Figure 1. The tandem [4+2]/allylboration three-component reaction involving simple 1-boronobutadienes.

Several other laboratories have studied this versatile tandem reaction,[3] including applications towards the synthesis of complex natural products.[3f]

The main drawback of 1-boronobutadienes stems from the steric and electronic deactivating effect of the boronate substituent and the consequent need for highly activated dienophiles as cycloaddition partners (e.g. maleic anhydride, maleimides). A number of approaches have been devised to overcome the electron-deactivating effect of the boronate group by the formation of ate adducts,[4] by using Lewis acids to activate the dienophile,[3d] or through the intermediacy of intramolecular approaches.[5] Herein, we describe our approach to address this reactivity issue. We sought to examine the effect of electron-donating ether substituents to counterbalance the deleterious effect of the boronate group on the butadiene framework. In principle, the use of dienes of type I–III in the [4+2]/allylboration tandem reaction will allow access to a number of new, oxygenated cyclohexene derivatives with a stereodefined hydroxyalkyl substituent. This preliminary communication describes the preparation and evaluation of dienes **1** and **2** in the Vaultier tandem reaction.



I II III

1 $(RO)_2$ = pinacolate, R' = Me

2 $(RO)_2$ = pinacolate, R' = Et_3Si

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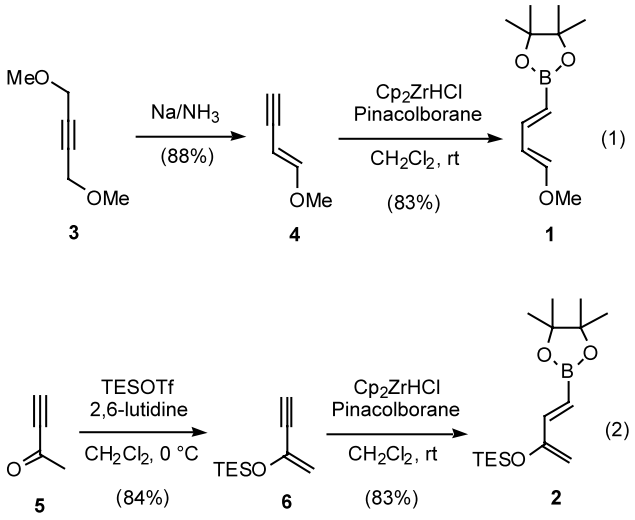
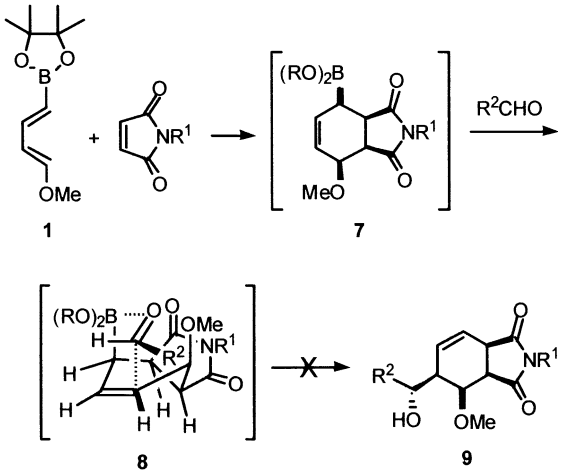
The preparation of dienes **1** and **2**, highlighted in Scheme 1, featured a chemoselective zirconocene-catalyzed hydroboration of enynes as a key step.[6] For diene **1** (1-borono-4-methoxybutadiene pinacolate), enyne precursor **4** was obtained following treatment of **3** with sodium in ammonia (Eq. (1)). Then, a zirconocene-catalyzed pinacolboration of **4** furnished boronobutadiene **1** in 73% overall yield.[7] Diene **2** (1-borono-3-triethylsiloxybutadiene pinacolate) was prepared in analogous fashion using enyne **6** (Eq. (2)).[7,8] Both dienes can be prepared in gram scale and can be kept in the fridge (5°C) for a few weeks.



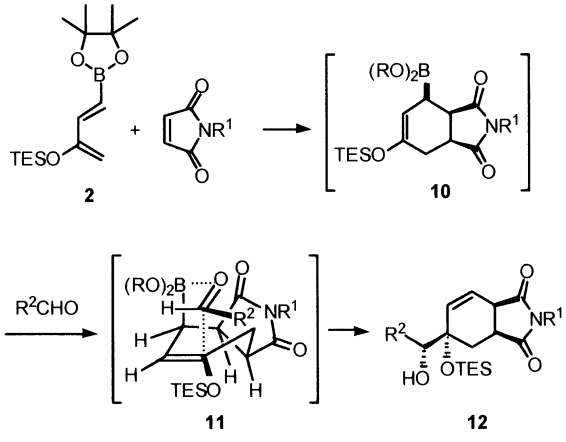
Scheme 1.

The boronobutadienes **1** and **2** were first tested in a model one-pot [4+2]/allylboration protocol involving various dienophiles and benzaldehyde as the aldehyde component. From these studies, it was found that diene **1** can undergo the first step with typical dienophiles (maleimides, methyl acrylate) and provide [4+2] cycloadducts **7** at relatively high temperature (toluene, 80°C), but the latter failed to provide allylboration products (**9**) even at higher temperatures (up to 120°C, where decomposition was observed) (Scheme 2). All attempts to promote the allylboration with Lewis acids[9] were in vain. A possible explanation to rationalize the failure of intermediates **7** to undergo the allylboration step is the significant steric crowding caused by the methoxy group on the (top) concave face of the putative transition structure **8**. The possible occurrence of internal coordination between the methoxy oxygen and the boronate group may also inhibit coordination of the aldehyde substrate.



Scheme 2.

Diene **2**, on the other hand, did provide the expected end-products **12** from the [4+2]/allylboration reaction (Scheme 3). The optimal one-pot procedure involved stirring the three reactants in almost equimolar fashion in toluene at 80–100°C for 16–24 h. Only doubly activated dienophiles (*N*-phenyl and *N*-methyl maleimide) reacted efficiently. Nonetheless, substrate generality for the aldehyde component is excellent, as shown by the range of aliphatic and aromatic aldehydes (both electron-poor and electron-rich) of Table 1 that provided the desired products in good to high yields. All purified reaction products were fully characterized by NMR and MS.[10] Only a single diastereomer was observed and isolated in all cases. Stereochemical confirmation was obtained by X-ray crystal structure determination on **13**,[11] which was obtained by desilylation of **12f** (Eq. (1), Scheme 4). This confirmed that the relative stereochemistry in the products of tandem [4+2]/allylboration of diene **2**, as indicated in Scheme 3, mirrors that of the unactivated 1-boronobutadienes.[2,3]



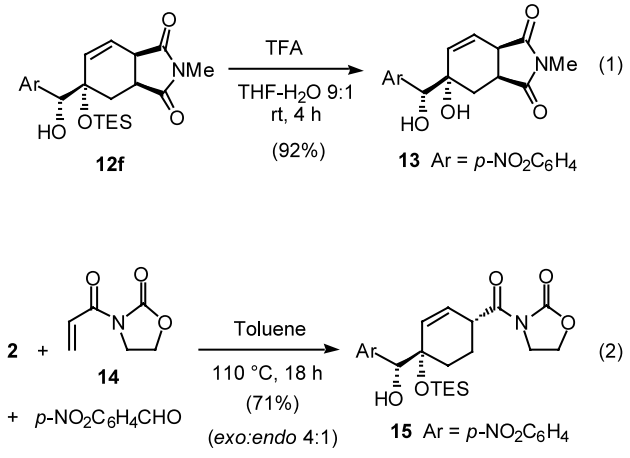
Scheme 3.

Mechanistically, the [4+2] cycloaddition of boronobutadiene **2** with maleimides is expected to proceed with complete *endo*-selectivity to give the allylboronate intermediate (**10**) shown in Scheme 3. From the latter, the stereochemical outcome of the allylation step can be explained via the usual cyclic chair-like allylboration transition structure (**11**) involving *anti* coordination of the aldehyde to the boronyl group oriented axially on the *endo* face of the cyclohexane ring.

Table 1. Tandem [4+2]/allylboration of diene **2** (Scheme 3)[a]

Entry	Dienophile (R^1)	Aldehyde (R^2)	T (°C)	Time (h)	Product	Yield (%)[b]
1	Ph	C_6H_5	80	16	**12a**	76
2	Ph	4-NO_2-C_6H_4	80	24	**12b**	92
3	Ph	4-MeO-C_6H_4	100	16	**12c**	82
4	Ph	4-Br-C_6H_4	80	16	**12d**	93
5	Ph	*i*-$PrCH_2$	80	24	**12e**	88
6	Me	4-NO_2-C_6H_4	80	24	**12f**	89
7	Me	4-MeO-C_6H_4	100	16	**12g**	67
8	Me	4-Br-C_6H_4	80	16	**12h**	78

[a] Typical reaction scale: approx. 1.0 mmol diene, 1.1 mmol dienophile, 1.1 mmol aldehyde, 1.0 M in toluene.
[b] Unoptimized yields of pure products isolated after flash chromatography.



Scheme 4.

Although methyl acrylate also reacted with diene **2** and *p*-NO_2-benzaldehyde, it led to a rather poor diastereomeric selectivity (*endo*:*exo* 2:3). The oxazolidinone derivative **14**, however, proved to be effective and provided a better level of selectivity in the formation of *exo* product **15** with a 71% yield (Eq. (2), Scheme 4).[12] This combination of substrates is very attractive in view of the fact that chiral catalysts are known to be effective in enantioselective cycloadditions of dienophile **14**.[13]

In conclusion, this study on the synthesis and behavior of dienes **1** and **2** in the Vaultier [4+2]/allylboration tandem reaction confirms the potential of these intermediates towards the stereoselective synthesis of hydroxyalkylated cyclohexene derivatives. Although these electronically enriched dienes have not demonstrated the anticipated increase of reactivity to employ moderately activated dienophiles (e.g. acrylates) at low temperature, different palliative strategies are being pursued in our laboratory. On the other hand, the success of the one-pot tandem reaction with dienophile **14** provides a new stereoselective approach to polysubstituted cyclohexene intermediates with potential use in the synthesis of complex natural products. To this end, the use of chiral catalysts with dienophile **14** will be examined in order to achieve this powerful tandem reaction in a highly enantioselective fashion.[13]

Acknowledgements

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7. Characterization data for dienes **1** and **2**. Compound **1**: IR (neat) 2978, 2838, 1644, 1607 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.82 (dd, 1H, $J=17.6$ Hz, $J=10.7$ Hz), 6.76 (d, 1H, $J=12.5$ Hz), 5.60 (dd, 1H, $J=12.5$ Hz, $J=10.7$ Hz), 5.34 (d, 1H, $J=17.6$ Hz), 3.60 (s, 3H), 1.40 (s, 12H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 154.9, 147.1, 107.7, 82.8, 56.5, 24.8. HRMS (EI) m/z calcd for $C_{11}H_{19}BO_3$: 210.1427. Found: 210.1429.
Compound **2**. IR (neat) 2957, 2878, 1626, 1588 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.80 (d, 1H, $J=17.7$ Hz), 5.86 (d, 1H, $J=17.7$ Hz), 4.44 (s, 1H), 4.42 (s, 1H), 1.26 (s, 12H), 0.96 (t, 9H, $J=7.8$ Hz), 0.64 (q, 6H, $J=7.8$ Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 147.0, 98.4, 83.2, 24.8, 6.8, 5.0. HRMS (EI) m/z calcd for $C_{16}H_{32}O_3BSi$: 311.2208. Found: 311.2207.

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10. Characterization data for bicyclic compounds **12**: Compound **12a**. Mp 155–156°C; IR (KBr) 3489, 3062, 3032, 2953, 2874, 1778, 1708, 1598 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.20–7.48 (m, 10H), 6.10 (dd, 1H, $J=10.2$ Hz, $J=4.2$ Hz), 5.92 (dd, 1H, $J=10.2$ Hz, $J=2.5$ Hz), 4.40 (d, 1H, $J=3.8$ Hz), 3.60 (m, 1H), 3.34 (m, 1H), 2.36–2.44 (m, 2H), 1.88 (dd, 1H, $J=13.8$ Hz, $J=7.5$ Hz), 0.84 (t, 9H, $J=7.8$ Hz), 0.56 (q, 6H, $J=7.8$ Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 178.1, 175.2, 139.3, 135.5, 131.7, 129.1, 128.6, 127.9, 127.7, 127.6, 126.3, 123.6, 79.3, 73.7, 40.7, 36.8, 31.0, 7.1, 6.7. HRMS (ESI) m/z calcd for $C_{27}H_{33}NO_4NaSi$ $[M+Na]^+$: 486.2071. Found: 486.2079. Anal. calcd for $C_{27}H_{33}NO_4Si$: C, 69.94; H, 7.17; N, 3.02. Found: C, 69.75; H, 7.30; N, 3.03%.
Compound **12b**. Mp 182–183°C; IR (KBr) 3477, 2954, 2909, 2875, 1778, 1708, 1599 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.18 (d, 2H, $J=8.8$ Hz), 7.24–7.54 (m, 7H), 6.20 (dd, 1H, $J=10.2$ Hz, $J=4.3$ Hz), 5.82 (dd, 1H, $J=10.2$ Hz, $J=2.2$ Hz), 4.46 (d, 1H, $J=5.4$ Hz), 3.66 (m, 1H), 3.16 (m, 1H), 2.68 (m, 2H), 1.80 (dd, 1H, $J=14.2$ Hz, $J=7.8$ Hz), 0.84 (t, 9H, $J=7.7$ Hz), 0.58 (q, 6H, $J=7.7$ Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 177.9, 175.0, 147.4, 146.4, 135.5, 131.6, 129.2, 129.0, 128.7, 126.1, 124.6, 122.6, 78.3, 73.6, 40.5, 36.8, 29.8, 7.1, 6.6. HRMS (ESI) m/z calcd for $C_{27}H_{32}N_2O_6NaSi$ $[M+Na]^+$: 531.1922. Found: 531.1922. Anal. calcd for $C_{27}H_{32}N_2O_6Si$: C, 63.76; H, 6.34; N, 5.51. Found: C, 63.75; H, 6.25; N, 5.40%.
Compound **12c**. Mp 169–170°C; IR (KBr) 3489, 2953, 2909, 2874, 2778, 1710, 1611 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.18–7.50 (m, 7H), 6.80 (d, 2H, $J=8.8$ Hz), 6.10 (dd, 1H, $J=10.3$ Hz, $J=4.0$ Hz), 5.96 (dd, 1H, $J=10.3$ Hz, $J=1.5$ Hz), 4.38 (d, 1H, $J=4.9$ Hz), 3.78 (s, 3H), 3.6 (m, 1H), 3.32 (m, 1H), 2.28–2.40 (m, 2H), 1.88 (dd, 1H, $J=13.5$ Hz, $J=6.0$ Hz), 0.88 (t, 9H, $J=7.7$ Hz), 0.58 (q, 6H, $J=7.7$ Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 178.1, 175.2, 159.1, 135,4, 131.7, 131.4, 129.1, 128.9, 128.5, 126.3, 123.6, 113.1, 78.9, 73.8, 55.3, 40.8, 36.8, 31.3, 7.2, 6.7. HRMS (ESI) m/z calcd for $C_{28}H_{35}NO_5NaSi$ $[M+Na]^+$: 516.2177. Found: 516.2178. Anal. calcd for $C_{28}H_{35}NO_5Si$: C, 68.12; H, 7.15; N, 2.84. Found: C, 68.13; H, 7.30; N, 2.83%.
Compound **12d**. Mp 145–147°C; IR (KBr) 3484, 3065, 2953, 2909, 2874, 1777, 1708, 1597 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 7.18–7.45 (m, 9H), 6.14 (dd, 1H, $J=10.2$ Hz, $J=4.2$ Hz), 5.86 (dd, 1H, $J=10.2$ Hz, $J=2.5$ Hz), 4.36 (d, 1H, $J=5.2$ Hz), 3.62 (m, 1H), 3.32 (m, 1H), 2.40 (m, 2H), 1.82 (dd, 1H, $J=13.5$ Hz, $J=7.3$ Hz), 0.86 (t, 9H, $J=8.1$ Hz), 0.58 (q, 6H, $J=8.1$ Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 178.0, 175.1, 138.2, 135.5, 131.7, 130.6, 129.7, 129.2, 128.6, 126.2, 124.0, 121.7, 78.5, 73.5, 40.6, 36.8, 30.4, 7.1, 6.7. HRMS (ESI) m/z calcd for $C_{27}H_{32}NO_4NaSiBr$ $[M+Na]^+$: 564.1176. Found: 564.1177. Anal. calcd for $C_{27}H_{32}NO_4SiBr$: C, 59.77; H, 5.95; N, 2.58. Found: C, 59.82; H, 5.86; N, 2.57%.
Compound **12e**. Mp 109–111°C; IR (KBr) 3514, 2954, 2874, 1782, 1711, 1599 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.22–7.42 (m, 5H), 6.12 (dd, 1H, $J=10.2$ Hz, $J=4.0$ Hz), 5.96 (dd, 1H, $J=10.2$ Hz, $J=2.3$ Hz), 3.60 (m, 1H), 3.28 (m, 2H), 2.16 (dd, 1H, $J=13.6$ Hz, $J=7.2$ Hz), 1.96 (dd, 1H, $J=13.6$ Hz, $J=7.2$ Hz), 1.76 (m, 2H), 1.30–1.44 (m, 2H), 0.78–0.96 (m, 15H), 0.56 (t, 6H, $J=7.8$ Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 178.3, 175.1, 135.9, 131.7, 129.1, 128.5, 126.3, 123.8, 75.2, 73.6, 40.8, 39.5, 36.8, 30.6, 25.0, 24.1, 21.6, 7.2, 6.8. HRMS (ESI) m/z calcd for $C_{25}H_{37}NO_4NaSi$ $[M+Na]^+$: 466.2384. Found: 466.2383. Anal. calcd for $C_{25}H_{37}NO_4Si$: C, 67.68; H, 8.41; N, 3.16. Found: C, 67.75; H, 8.63; N, 3.09%.
Compound **12f**. Mp 180–181°C; IR (KBr) 3461, 2954, 2910, 2875, 1776, 1698, 1604, 1519, 1436 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.18 (d, 2H, $J=8.8$ Hz), 7.44 (d, 2H, $J=8.8$ Hz), 6.08 (dd, 1H, $J=10.2$ Hz, $J=4.3$ Hz), 5.78 (dd, 1H, $J=10.2$ Hz, $J=2.4$ Hz), 4.36 (d, 1H, $J=5.1$ Hz), 3.46 (m, 1H), 3.18 (m, 1H), 3.00 (s, 3H), 2.58 (d, 1H, $J=5.6$ Hz), 2.38 (dd, 1H, $J=14.1$ Hz, $J=5.7$ Hz), 1.76 (dd, 1H, $J=14.1$ Hz, $J=7.7$ Hz), 0.84 (t, 9H, $J=7.8$ Hz), 0.58 (q, 6H, $J=7.8$ Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 179.0, 176.0, 147.4, 146.6, 134.9, 128.8, 124.7, 122.5, 78.3, 73.6, 40.6, 36.7, 30.2, 25.2, 7.0, 6.6. HRMS (ESI) m/z calcd for $C_{22}H_{30}N_2O_6NaSi$ $[M+Na]^+$: 469.1765. Found: 469.1766. Anal. calcd for $C_{22}H_{30}N_2O_6Si$: C, 59.17; H, 6.77; N, 6.27. Found: C, 59.12; H, 6.70; N, 6.11%.
Compound **12g**. Mp 95–96°C; IR (KBr) 3477, 2953, 2909, 2874, 1775, 1698, 1611, 1584 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.16 (d, 2H, $J=8.7$ Hz), 6.78 (d, 2H, $J=8.7$ Hz), 6.02 (dd, 1H, $J=10.3$ Hz, $J=3.5$ Hz), 5.94 (dd, 1H, $J=10.3$ Hz, $J=2.1$ Hz), 4.16 (s, 1H), 3.68 (s, 3H), 3.40 (m, 1H), 3.16 (m, 1H), 2.96 (s, 3H), 2.18 (s, 1H), 2.04 (dd, 1H, $J=13.6$ Hz, $J=8.0$ Hz), 1.84 (dd, 1H, $J=13.6$ Hz, $J=7.3$ Hz), 0.86 (t, 9H, $J=7.8$ Hz), 0.44 (q, 6H, $J=7.8$ Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 179.2, 176.2, 159.1, 134.7, 131.5, 128.8, 123.7, 113.1, 79.1, 73.8, 55.3, 40.8, 36.6, 31.6, 25.0, 7.2, 6.7. HRMS (ESI) m/z calcd for $C_{23}H_{33}NO_5NaSi$ $[M+Na]^+$: 454.2020. Found: 454.2026. Anal. calcd for $C_{23}H_{33}NO_5Si$: C, 64.00; H, 7.71; N, 3.25. Found: C, 63.81; H, 7.77; N, 3.25%.
Compound **12h**. Mp 160–161°C; IR (KBr) 3466, 2953, 2909, 2875, 1776, 1698, 1486 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.40(d, 2H, $J=8.6$ Hz), 7.14 (d, 2H, $J=8.6$ Hz), 6.04 (dd, 1H, $J=10.2$ Hz, $J=4.1$ Hz), 5.84 (dd, 1H, $J=10.2$ Hz, $J=2.5$ Hz), 4.24 (d, 1H, $J=4.8$ Hz), 3.44 (m, 1H), 3.16 (m, 1H), 2.99 (s, 3H), 2.44 (d, 1H, $J=5.0$ Hz), 2.20 (dd, 1H, $J=13.8$ Hz, $J=6.4$ Hz), 1.80 (dd, 1H, $J=13.8$ Hz, $J=7.4$ Hz), 0.84 (t, 9H, $J=7.8$ Hz), 0.44 (q, 6H, $J=7.8$ Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 179.1, 176.1, 138.2, 134.7, 130.6, 129.5, 124.1, 78.7, 73.6, 40.7, 36.6, 30.9, 25.1, 7.1, 6.6. HRMS (ESI) m/z calcd for $C_{22}H_{30}NO_4NaSi$ $[M+Na]^+$: 502.1020. Found: 502.1024. Anal. calcd for $C_{22}H_{30}NO_4Si$: C, 55.00; H, 6.27; N, 2.92. Found: C, 54.79; H, 6.09; N, 2.84%.
11. Data (excluding structure factors) for this structure have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-197493. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

12. The two diastereomers were separable by flash-chromatography. The *exo* stereochemistry of the major isomer was tentatively determined from the coupling constants of the allylic hydrogen obtained by selective proton NMR decoupling experiments. Characterization data for the major *exo* isomer of compound **15**. Oil; IR (KBr) 3506, 2954, 2875, 1776, 1699, 1604, 1519, 1478 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.16 (d, 2H, $J=8.9$ Hz), 7.44 (d, 2H, $J=8.9$ Hz), 5.88 (dd, 1H, $J=10.3$ Hz, $J=3.4$ Hz), 5.38 (dd, 1H, $J=10.3$ Hz, $J=2.1$ Hz), 4.58 (s, 1H), 4.41 (t, 2H, $J=8.1$ Hz), 4.18 (m, 1H), 3.98 (m, 2H), 2.08 (m, 1H), 1.96 (m, 2H), 1.78 (m, 1H), 0.86 (t, 9H, $J=7.8$ Hz), 0.58 (q, 6H, $J=7.8$ Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.9, 153.1, 147.7, 147.2, 133.4, 128.7, 128.4, 122.5, 77.8, 75.2, 62.1, 42.9, 39.4, 30.1, 22.7, 7.1, 6.5. HRMS (ESI) m/z calcd for $C_{23}H_{32}N_2O_7NaSi$ $[M+Na]^+$: 499.1871. Found: 499.1875. Anal. calcd for $C_{23}H_{32}N_2O_7Si$: C, 57.96; H, 6.77; N, 5.87. Found: C, 58.04; H, 6.70; N, 5.50%.

13. Evans, D. A.; Miller, S. J.; Lectka, T. *J. Am. Chem. Soc.* **1993**, *115*, 6460–6461.