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Stereocontrolled synthesis of all-*syn* 3,4-disubstituted L-prolines: studies of the reductive rearrangement of unactivated tertiary allylic alcohols

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ABSTRACT

We describe a stereocontrolled method that converts tertiary allylic alcohols in pyrrolidine-2-carboxylic acid derivatives prepared from 3-(*S*)-hydroxy-L-proline to all-*syn* 3,4-disubstituted L-prolines. A study of various parameters to optimize the reductive rearrangement of tertiary allylic alcohols to tetrasubstituted olefins was conducted.

1. Introduction

Substituted pyrrolidines are prevalent in the structures of many natural products as single units or as bicyclic to polycyclic variants.[1] Although many syntheses have been reported over the years, very few have addressed methods that lead to an all-*syn* orientation of substituents as precursor chirons that can be elaborated into more complex natural products. Representative structures of complex alkaloids harboring a substituted pyrrolidine as an embedded core azacycle are shown in Fig. 1.[2] Facile and stereocontrolled access to such motifs could be useful in the synthesis of alkaloids, and constrained peptidomimetics[3] with predetermined stereochemistry of substituents.

In connection with our efforts toward the synthesis of the tetracyclic core of daphniglaucin C and related azacyclic molecules,[4] we considered exploiting the versatile chemistry of enaminones derived from 3-(*S*)-hydroxy-L-proline represented by the generic structure **A** (Scheme 1). Well-known attack of various nucleophiles at the 4-position of these enaminones,[5] followed by a second Grignard reagent addition on the resulting α,β-unsaturated ketone, could generate a generic tertiary allylic alcohol (**B**). Stereoselective reductive removal of the allylic alcohol would lead to an all-*syn* orientation of appended substituents shown as **C**.

In pursuing this approach, our attention was drawn to a reported allylic alcohol deoxygenation of a substituted L-proline ester (**4**) in the presence of 5 mol % Pd/C in EtOAc under 1 atm of hydrogen, by Camplo and co-workers[6] (Scheme 2), which led to the syn-product **5** resulting from hydrogenolysis. This was rationalized on the basis of steric arguments favoring the

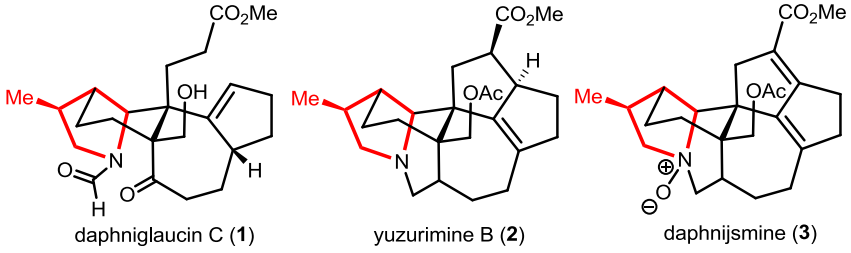

Fig. 1. Representative examples of complex alkaloids showing embedded 4-(*S*)-pyrrolidine motifs.

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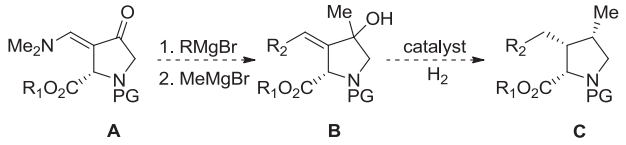
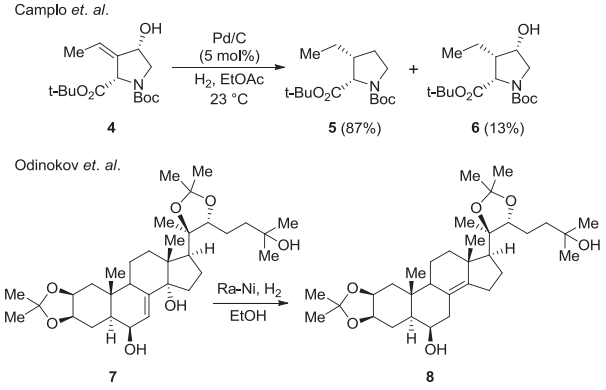


Scheme 1. Strategy toward the synthesis of 3,4-disubstituted L-prolines.

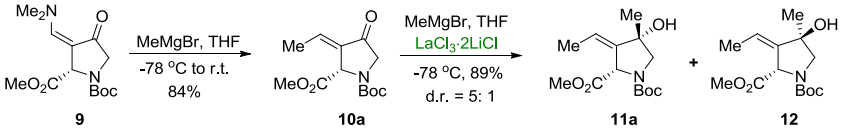


Scheme 2. Previous reports on allylic alcohol deoxygenation.

hydrogenolysis of the allylic alcohol rather than the expected reduction of the alkylidene appendage. In an independent study on cholesteroids by Odinokov and co-workers,[7] an allylic diol (**7**) was subjected to deoxygenation at the tertiary alcohol position with transposition of the double bond in the presence of Raney nickel in EtOH under 1 atm of hydrogen to give the tetrasubstituted steroid **8** in an unspecified yield.

2. Results and discussion

Addition of MeMgBr to enaminone **9**, readily available from 3-hydroxy-L-proline[4] led to the enone **10a** in 84% yield (Scheme 3). A second Grignard addition following the protocol of Knochel and co-workers[8] proceeded in a 1,2-fashion to furnish chemoselectively the allylic alcohols **11a** and **12** as a 5:1 diastereomeric mixture.



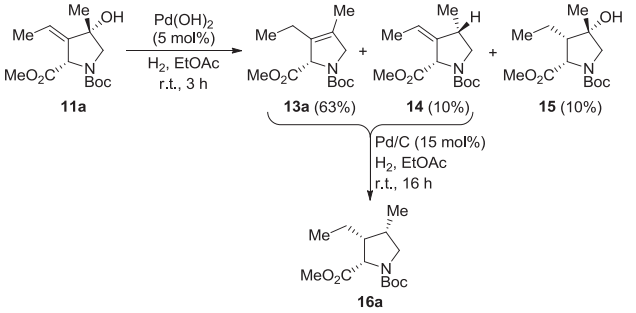
Scheme 3. Synthesis of the test alcohols **11a** and **12** from **9**.

We then undertook a systematic study of different catalysts and conditions in order to convert **11a** into the corresponding all-*syn*-2,3-substituted-L-proline derivative (Scheme 4). In the presence of $Pd(OH)_2/C$ (Pearlman's catalyst),[9] the major product was found to be the tetrasubstituted alkene **13a** (63%), accompanied by its exocyclic regioisomer **14** (10%) and the saturated alcohol **15** (10%). It is noteworthy that alkene **13a** could not be hydrogenated in situ to the intended **16a**, even after hydrogenation with $Pd(OH)_2/C$ for 48 h. However, isolating the tetrasubstituted alkene **13a** and subjecting it to hydrogenation in the presence of 15 mol % Pd/C afforded the all-*syn*-L-proline derivative **16a** in quantitative yield (Scheme 4). Moreover, when the alkene regioisomer **14** was submitted to the original reaction conditions ($Pd(OH)_2/C$, H_2, EtOAc), isomerization of the double bond to alkene **13a** occurred quantitatively.[10] However, the reverse isomerization from **13a** to **14** was not possible under the same conditions. When allowing the hydrogenation with $Pd(OH)_2/C$ to take place for 16 h, it was noted that none of the isomer **14** was observed, while an improved 68% yield of **13a** was obtained.

To further understand the requirements of the transformation in Scheme 4, a catalyst screening was conducted (Table 1). The results showed that the reaction requires a Pd-based catalyst.[11] Wilkinson's, Crabtree's, Lindlar's catalysts and, more surprisingly, Raney nickel, failed to yield any of the desired transposed alkene **13a**, and starting **11a** could be recovered (Table 1, entries 1–6). PtO_2 gave exclusively the reduced alcohol **15** (Table 1, entry 7).

The results shown in entries 8–11 seemed to imply that the transformation involves Pd(0) and not Pd(II)[12]. However, in the presence of 5 mol % Pd/C in EtOAc, only the saturated compound **15**, in which deoxygenation had not occurred, was isolated in 95% yield (Table 1, entry 12). Nevertheless, when lowering the loading of the catalyst (Table 1, entries 13–17), the deoxygenation product **13a** was observed, albeit in lower yields compared to entries with Pearlman's catalyst (Table 1, entries 1 and 2).

Next, we studied the influence of reducing agents on the reactions. Firstly, when using ammonium formate,[13] no reaction could be observed, even after heating at reflux in MeOH for three days and using catalyst loadings as high as 20 mol % (Table 2, entry 1). However, better yields, chemoselectivity and shorter reaction times were observed in the presence of Et_3SiH[14] (Table 2, entries 2–5, as compared to Table 1, entry 2). Although similar results were obtained using the benign and cheaper polymethylhydroxysilane (PMHS, Table 2, entries 5–7),[15] Et_3SiH was preferred for practical reasons.[16]



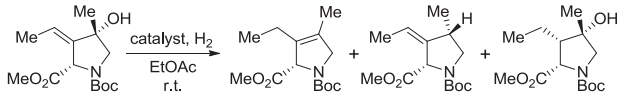
Scheme 4. Allylic hydrogenolysis toward all-*syn* 3,4-disubstituted L-prolines.

Next, a mechanistic study was conducted in order to assess the potential use of this strategy toward the synthesis of trisubstituted pyrrolines and pyrrolidines. In the first place, the allylic alcohol **12** (diastereomer of **11a**) was subjected to the allylic transposition conditions (Scheme 5). To our surprise, no transformation could be observed, even after adding 20 mol % $Pd(OH)_2/C$ and carrying out the reaction over several days.

Next, a deuteration experiment in the presence of Pearlman's catalyst with D_2 instead of H_2 afforded monodeuteration products **17** and **18** in a diastereoselective manner. The CD_3-analog **19** was also prepared and subjected to the hydrogenolysis conditions to give **20** in 68% yield without any loss of deuterium atoms. Furthermore, the acetylated alcohol **21** was subjected to the reductive transposition conditions and gave the same alkene **13a** in 73% yield.

Several proposed mechanisms for Pd-catalyzed hydrogenolysis of benzylic alcohols have been reported.[17] In contrast, examples of allylic alcohols are scarce. Considering the nature of the products and the aforementioned experiments (Scheme 5), two plausible

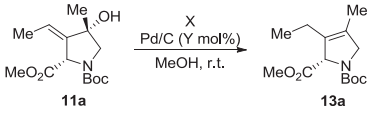
Table 1
Metal source screening



Entry	Catalyst	mol (%)	Time	**13a** (%)	**14** (%)	**15** (%)
1	$Pd(OH)_2/C$	5	3 h	63	10	10
2	$Pd(OH)_2/C$	5	16 h	68	—	10
3	$RhCl(PPh_3)_3$	5	3 d	n.r.		
4	$[Ir(cod)(PCy_3)(py)]PF_6$	5	3 d	n.r.		
5	Raney nickel	5	3 d		n.r.[d]	
6	Lindlar's catalyst	5	24 h	n.r.		
7	PtO_2	5	16 h	—	—	98
8	$PdCl_2$	5	2 d	Traces[a]		—
9	$Pd(OAc)_2$	5	4 d	Traces[a]		—
10	$Pd(OAc)_2+PPh_3$	5	4 d	39	18	—
11	Pd_2dba_3	5	3 d	60	15	20
12	Pd/C	5	1 h	—	—	95
13	Pd/C	1	1 h	9	—	87
14	Pd/C	0.25	16 h	Traces[a]		
15	Pd/C	0.5	16 h	11	—	34
16	Pd/C	0.5[b]	16 h	13	—	39
17	Pd/C	0.5[c]	2 d	25	—	23

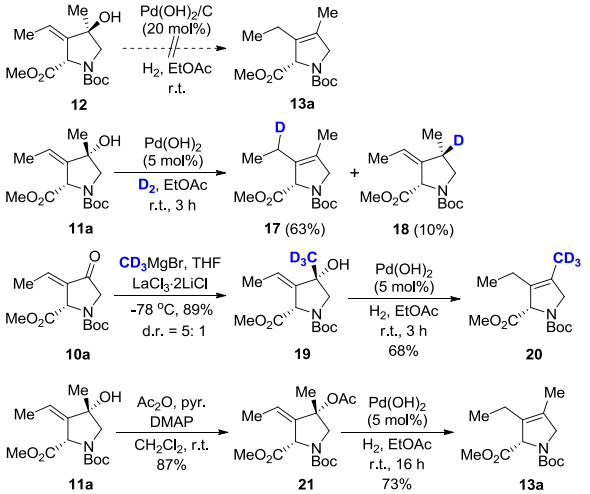
Solvent concentration used is 0.2 M unless mentioned otherwise.
[a] Visible TLC traces.
[b] Solvent concentration: 0.1 M.
[c] Solvent concentration: 0.05 M.
[d] Also tried in MeOH.

Table 2
Reducing agents screening



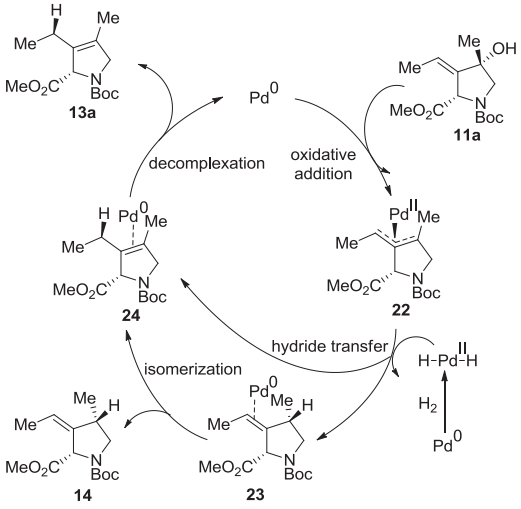
Entry	X	Y	Time	**13a** (%)
1	HCO_2NH_4, 10 equiv	5	3 d	n.r.
2	Et_3SiH, 5 equiv	5	40 min	78[a]
3	Et_3SiH, 10 equiv	1	40 min	78[a]
4	Et_3SiH, 5 equiv	1	40 min	82
5	**Et_3SiH, 2 equiv**	**1**	**40 min**	**82**
6	PMHS, 10 equiv	1	40 min	80
7	PMHS, 5 equiv	1	40 min	80
8	PMHS, 2 equiv	1	40 min	80

Bold highlights the optimal results.
Solvent concentration used is 0.2 M.
[a] Some side-products were observed in trace amounts.



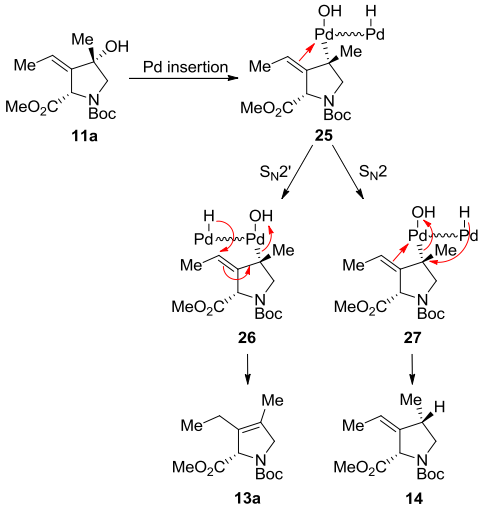
Scheme 5. Experiments conducted in order to study the mechanism.

pathways can be proposed for the reductive rearrangement. The first would involve a Tsuji–Trost type mechanism,[18] where water molecules contained in the wet commercial catalyst could facilitate the leaving of the hydroxyl group via a reported H-bond activation of the allylic alcohol.[19] After the formation of the π-allyl intermediate **22**, a hydride from a neighboring Pd atom would act as a nucleophile, thus affording products **13a** and **14** as shown in Scheme 6. The formation of the π-allyl complex would only be possible if palladium was coordinated anti to the leaving hydroxyl group, which implies that it would come from the upper face of the *N*-Boc L-proline ester derivative **11a**. This would explain the diastereoselectivity of the transformation, as only one diastereoisomer of **14** is observed (see Schemes 4 and 5).



Scheme 6. Tsuji–Trost type mechanism for the formation of **13a** and **14**.

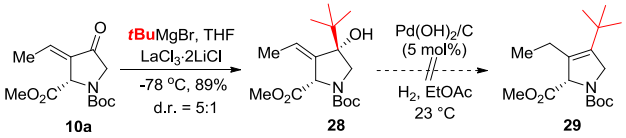
The second possible pathway would be a McQuillin-type hydrogenolysis mechanism,[20] where a Pd insertion occurs in the C–O bond (Scheme 7), followed by a nucleophilic substitution with a hydride coordinated to the Pd surface, as in the Tsuji–Trost type mechanism.[18,19] For such a reaction, the nucleophilic substitution can occur in a S_N2 or S_N2' fashion. The S_N2 pathway would thus result in an inversion of stereochemistry, affording **14** with the observed stereochemistry. The palladium insertion in the C–O bond would have to take place on the same face as the alcohol, on



Scheme 7. McQuillin's hydrogenolysis mechanism.

the lower face of the molecule. This may be impeded by the ester group, which adopts a pseudoaxial orientation to avoid $A^{1,2}$ and $A^{1,3}$ strains.

The main difference between the two pathways is the faciality of the attack of the Pd. In order to differentiate between the two faces, the L-proline analog **28** was synthesized in which the steric hindrance on the upper face was increased by introducing a *tert*-butyl group instead of the methyl group (Scheme 8). No reaction was observed with **28** in the presence of $Pd(OH)_2/C$ (5 mol %) under 1 atm hydrogen, which would suggest increased steric hindrance on the reactive upper face of the double bond. Moreover, recall that the allylic alcohol **12**, the diastereomer of **11a**, was also unreactive. The lower faces of **11a** and **12** are equally hindered by the ester group, although to a higher extent in **12** because of the methyl group. According to the π-allyl formation pathway (Scheme 6, structure **23**), the Pd would have to be coordinated anti to the hydroxyl group, which in the case of **12** would imply coordination on the lower hindered face of the exocyclic double bond. However, if the McQuillin type hydrogenolysis mechanism were implied, the insertion of the Pd in the C–O bond of **12** on the upper face will not be problematic from a steric point of view. The unreactivity of **12** suggests once again that the Pd needs to be coordinated anti to the hydroxyl group as in the proposed Tsuji–Trost type mechanism.



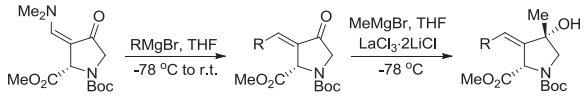
Scheme 8. No reaction with **28** toward reductive transposition conditions.

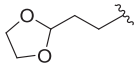
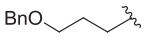
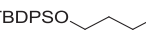
Another pathway could involve a concerted 'ene'-type mechanism, where the palladium would first coordinate to the alcohol followed by a transfer of a hydride to the double bond through a six-membered ring transition state. This mechanism was dismissed after the reaction was carried on the acetate ester **21**, and the olefin **13a** was obtained in 73% yield (Scheme 5), since the Pd–O(H)R coordination is theoretically impossible in this case. However, it is possible that another mechanistic pathway may be involved for the transformation of **21** to **13a** (Scheme 5). Nevertheless, and more importantly, this concerted 'ene' pathway would not account for the formation of the regioisomeric alkene **14**.

The possibility of the formation of an allylic carbocations was also considered. The delocalized carbocations could be subjected to a 'hydride' attack occurring at two positions, giving **13a** and **14** as products. Nonetheless, attempts to trap transient carbocations with methanol and aniline as nucleophiles were unsuccessful and this mechanism was not considered any further. Lastly, another pathway could be derived from the formation of a diene upon elimination of the tertiary alcohol, either from a carbocation undergoing an E_1 elimination or a direct E_2 elimination that could be hydrogenated to yield products **13a** and **14**. This pathway to an intermediate exocyclic methylene intermediate was ruled out since the product resulting from the reduction of **19**, a deuterated methyl analog of **11a**, retained the CD_3 group (Scheme 5). Furthermore, reduction in the presence of deuterium gas afforded monodeuterated products **17** and **18**, rather than multiply deuterated products arising from a presumed diene.[21]

In order to evaluate the applicability of the strategy in the synthesis of *syn*-substituted 3,4-L-proline analogs, the scope of the reaction was next studied for a selection of side-chains. From the known enaminone **9**, different nucleophiles were used to generate a selection of enones (**10b–j**, then allylic alcohols (**11b–j**, Table 3), using the same protocol as described previously (Schemes 1 and 3).

Table 3
Synthesis of allylic alcohols **11a–i** for substrate scope study

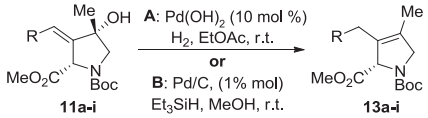


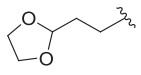
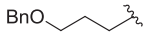
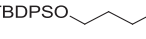
Entry	R	**10** (%)	**11** (%) (dr)[a]
1	Cyclopentyl (**b**)	59	78 (>20:1)
2	Decyl (**c**)	56	62 (>20:1)
3	 (**d**)	70	72 (5:1)
4	 (**e**)	84	89 (5:1)
5	 (**f**)	65	63 (>20:1)
6	Phenethyl (**g**)	52	91 (3:1)
7	Ph (**h**)	62	89 (15:1)
8	ρ-OMe–Ph (**i**)	59	74 (15:1)
9	ρ-F–Ph (**j**)	59	80 (15:1)

[a] Unlike **11a** and **12**, diastereoisomers were hardly separable for **11e**, and inseparable in all other cases. The dr was calculated upon integration of ^1H NMR signals.

With this selection of allylic alcohols in hand (**11a–j**), the allylic deoxygenation and double bond transposition was tested employing the two optimal methods developed (Table 4). It appeared that a change in the distal substituent of the exocyclic alkene resulted in a profound effect on the feasibility of the reaction, as well as the product distribution. Allylic alcohols bearing alkyl groups (Table 4, entries 1–6) led to allylic deoxygenation in acceptable yields in the presence of Pearlman's catalyst. Whereas a significant improvement was observed when using Et_3SiH in conjunction with Pd/C when R=Me or cyclopentyl (Tables 2 and 4), the opposite was observed in the case of compound **11e**, for which a complex mixture was observed (Table 4, entry 5).[4]

Table 4
Substrate scope for the reductive allylic transposition



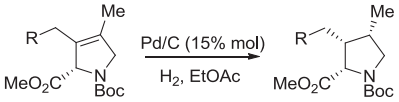
Entry	R	Method A (%)	Method B (%)
1	Methyl (**a**)	68	82
2	Cyclopentyl (**b**)	73	79[a]
3	Decyl (**c**)	68	62
4	 (**d**)	78	76[a]
5	 (**e**)	70[b]	Complex mixture
6	 (**f**)	70	54[a]
7	Phenethyl (**g**)	36[c]	50
8	Ph (**h**)	18[d]	47[d]
9	ρ-OMe–Ph (**i**)	25[d]	62[d]
10	ρ-F–Ph (**j**)	32[e]	Complex mixture

[a] Traces of the exocyclic alkene regioisomer were observed.
[b] With concomitant hydrogenolysis of the benzyl ether group.
[c] 37% of hydrogenated tertiary alcohol presumably analogous to **15** was isolated.
[d] The all-*syn* pyrrolidine was partly obtained as an inseparable by-product (>10% based on ^1H NMR).
[e] 45% of hydrogenated tertiary alcohol presumably analogous to **15** was isolated, and separated from the all-*syn* pyrrolidine analogous to **16a**.

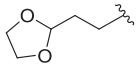
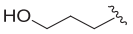
In the case of the phenethyl analog (Table 4, entry 7), modest yields of the desired tetrasubstituted alkene were obtained. Likewise, the phenyl and ρ-OMe–phenyl compounds (Table 4, entries 8 and 9) led to lower yields of the expected tetrasubstituted alkene, although using Pd/C with Et_3SiH afforded slightly better results. It is of interest that for those analogs, partial over-reduction to the corresponding pyrrolidine was observed leading to minor inseparable by-products. Finally, in the case of ρ-fluorophenyl-substituted pyrroline (Table 4, entry 10), a complex mixture was obtained when using triethylsilane with Pd/C, while hydrogen with $Pd(OH)_2/C$ led directly to a modest yield of the over-reduced all-*syn* 3,4-disubstituted L-proline.

In order to assess the ease with which this approach could be used to generate all-*syn* 3,4-disubstituted L-prolines, selected analogs were hydrogenated using Pd/C under 1 atm of hydrogen (Table 5, see Scheme 4). Hydrogenation was complete, clean and diastereoselective, affording the intended all-*syn* 3,4-disubstituted L-prolines in moderate to good yields (Table 5, entries 1–8).

Table 5
Hydrogenation to the all-*syn* 2,3,4-trisubstituted pyrrolidines



13a-i 16a-i

Entry	R	Yield (%)
1	Methyl (**a**)	quant
2	Cyclopentyl (**b**)	80
3	Decyl (**c**)	76
4	 (**d**)	70
5	 (**e**)	quant[4]
6	Phenethyl (**g**)	82
7	Ph (**h**)	70
8	ρ-OMe–Ph (**i**)	67

3. Conclusion

We have described a concise and stereocontrolled method to prepare all-*syn* 3,4-disubstituted L-proline analogs starting with 3-(*S*)-hydroxy-L-proline. Conversion to the corresponding *N*,*N*-dimethylamino enaminone, followed by conjugate attack with carbon nucleophiles led to the corresponding 1,4-adducts with elimination of dimethylamine. $LaCl_3$-mediated addition of MeMgBr to the ketone gave a mixture of the tertiary alcohols, which were subjected to a variety of catalytic and chemical reduction conditions. The tetrasubstituted Δ-3 pyrroline was isolated as a discrete intermediate, then further reduced to the intended all-*syn* *N*-Boc 3,4-disubstituted L-proline methyl esters. The process was exemplified by the synthesis of the 3-(*R*)-ethyl-4-(*R*)-methyl *N*-Boc L-proline methyl ester and related aliphatic and aromatic analogs. These compounds can be useful as versatile intermediates toward the synthesis of alkaloids and as constrained peptidomimetics with predetermined absolute stereochemistry.

4. Experimental section

4.1. General information

All non-aqueous reactions were run in flame-dried glassware under a positive pressure of argon with exclusion of moisture from reagents and glassware using standard techniques for manipulating air-sensitive compounds. Anhydrous solvents were obtained using standard drying techniques. Flash chromatography was performed on 230–400 mesh silica gel with the indicated solvent systems. Infrared spectra were recorded on a FT-IR spectrometer and are reported in reciprocal centimeters (cm^{-1}). All nuclear magnetic resonance spectra were recorded on a 400 MHz spectrometer. Chemical shifts are recorded in parts per million from tetramethylsilane with the solvent resonance as the internal standard. Accurate mass measurements were performed on a LC-MSDTOF instrument using fast atom bombardment (FAB) or electrospray ionization (ESI) techniques. Protonated molecular ions $(M+H)^+$ and/or sodium adducts $(M+Na)^+$ were used for empirical formula confirmation.

4.2. Typical procedure for synthesis of enones 10a–j

Under argon and in a flame-dried flask, a solution of the enaminone **9** (1 equiv) in dry THF (0.2 M) was cooled to −78 °C and treated with the given Grignard reagent (1.5 equiv) dropwise. After stirring for 1 h, the dry ice bath was removed and the reaction was allowed to warm to rt. It was stirred for 30 min at this temperature before a saturated aqueous solution of NH_4Cl was added slowly. The red biphasic mixture was separated and the aqueous phase was extracted three times with EtOAc. The combined organic layers were washed with brine and dried over Na_2SO_4, and the solvent was removed under reduced pressure.

*4.2.1. (S,E)-1-tert-Butyl 2-methyl 3-ethylidene-4-oxopyrrolidine-1,2-dicarboxylate (**10a**).* Obtained from the enaminone **9** (2.00 g, 6.71 mmol) using the general procedures. Purification of the residue by flash chromatography (hexanes/EtOAc=70/30) gave the title enone (1.51 g, 84%) as a thick colorless oil. $[\alpha]_D^{20}$ +80.1 (*c* 1.00, $CHCl_3$); IR (neat): ν_{max}=2978, 1747, 1705, 1659, 1436, 1394, 1368, 1317, 1259, 1167, 1120, 994, 902, 858, 773, 512 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), mixture of rotamers: δ=6.91 (1H, q, *J*=7.2 Hz), 5.28–5.19 (1H, 2s), 4.03–3.91 (2H, m), 3.73 (3H, br s), 2.00 (3H, d, *J*=7.2 Hz), 1.47–1.44 (9H, 2s); ^{13}C NMR (100 MHz, $CDCl_3$), mixture of rotamers: δ=196.5, 195.8, 169.9, 153.9, 153.0, 141.1, 137.7, 137.5, 132.4, 132.2, 80.8, 59.8, 59.1, 52.9, 52.5, 52.1, 52.0, 27.8, 27.8, 27.8, 15.0, 14.9; HRMS (ESIMS): calcd for $C_{13}H_{19}NO_5Na$ $[M+Na]^+$ 292.11652, found 292.11554.

*4.2.2. (S,E)-1-tert-Butyl 2-methyl 3-(cyclopentylmethylene)-4-oxopyrrolidine-1,2-dicarboxylate (**10b**).* Obtained from the enaminone **9** (2.00 g, 6.71 mmol) using the general procedures. Purification of the residue by flash chromatography (hexanes/EtOAc=80/20) gave the title enone (1.30 g, 59%) as a thick colorless oil. $[\alpha]_D^{20}$ +100.7 (*c* 1.00, $CHCl_3$); IR (neat): ν_{max}=2955, 1744, 1706, 1649, 1392, 1163, 1119, 1012 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), mixture of rotamers: δ=6.73–6.63 (1H, m), 5.29–5.19 (1H, 2s), 4.05–3.89 (2H, m), 3.73–3.71 (3H, 2s), 3.00–2.87 (1H, m), 1.93–1.84 (1H, m), 1.81–1.62 (5H, m), 1.46–1.44 (9H, 2s), 1.40–1.28 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$), mixture of rotamers: δ=197.5, 196.8, 170.9, 170.7, 154.3, 153.5, 147.6, 147.4, 129.8, 129.5, 81.2, 81.2, 60.3, 59.5, 53.4, 52.9, 52.7, 52.6, 40.2, 40.2, 33.1, 32.6, 32.5, 28.3, 28.2, 25.8, 25.8, 25.7; HRMS (ESIMS): calcd for $C_{17}H_{25}NO_5Na$ $[M+Na]^+$ 346.16249, found 346.16390.

*4.2.3. (S,E)-1-tert-Butyl 2-methyl 4-oxo-3-undecylidenepyrrolidine-1,2-dicarboxylate (**10c**).* Obtained from the enaminone **9** (1.20 g, 4.03 mmol) using the general procedures. Purification of the residue by flash chromatography (hexanes/EtOAc=90/10) gave the title enone (880 mg, 56%) as a thick colorless oil. $[\alpha]_D^{20}$ +78.9 (*c* 1.00, $CHCl_3$); IR (neat): ν_{max}=2930, 2861, 1747, 1656, 1460, 1439, 1394, 1371, 1321, 1258, 1203, 1163, 1121, 1019, 907, 862, 775, 739, 632 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), mixture of rotamers: δ=6.81

(1H, br s), 5.25–5.16 (1H, 2s), 4.02–3.92 (2H, m), 3.70 (3H, s), 2.38–2.30 (2H, m), 1.46–1.40 (11H, 2s), 1.24 (14H, br s), 0.87–0.83 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$), mixture of rotamers: δ=197.2, 196.5, 170.5, 154.3, 153.4, 143.3, 143.0, 131.6, 131.3, 81.2, 81.2, 60.3, 59.6, 53.3, 52.9, 52.5, 52.4, 31.8, 29.5, 29.5, 29.4, 29.3, 28.2, 28.2, 28.1, 22.6, 14.0; HRMS (ESIMS): calcd for $C_{22}H_{37}NO_5Na$ $[M+Na]^+$ 418.25639, found 418.25722.

*4.2.4. (S,E)-1-tert-Butyl 2-methyl 3-(3-(1,3-dioxolan-2-yl)propylidene)-4-oxopyrrolidine-1,2-dicarboxylate (**10d**).* Obtained from the enaminone **9** (1.20 g, 4.03 mmol) using the general procedures with 3 equiv of Grignard reagent.[22] Purification of the residue by flash chromatography (hexanes/EtOAc=70/30) gave the title enone (1.00 g, 75%) as a thick colorless oil. $[\alpha]_D^{20}$ +52.9 (*c* 1.00, $CHCl_3$); IR (neat): ν_{max}=3464, 2977, 1746, 1704, 1394, 1162, 1034, 916, 857, 773, 734, 648, 597 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), mixture of rotamers: δ=6.85 (1H, td, *J*=7.8, 2.1 Hz), 5.32–5.23 (1H, 2s), 4.94–4.90 (1H, m), 4.07–3.92 (4H, m), 3.87–3.82 (2H, m), 3.76–3.75 (3H, 2s), 2.56–2.48 (2H, m), 1.88–1.81 (2H, m), 1.50–1.47 (9H, 2s); ^{13}C NMR (100 MHz, $CDCl_3$), mixture of rotamers: δ=197.2, 196.5, 170.4, 154.3, 153.5, 142.2, 142.0, 131.8, 131.5, 103.3, 81.3, 81.3, 65.1, 65.0, 60.2, 59.5, 53.4, 52.9, 52.6, 52.5, 32.0, 32.0, 28.3, 28.3, 24.1, 24.0; HRMS (ESIMS): calcd for $C_{17}H_{25}NO_7Na$ $[M+Na]^+$ 378.15109, found 378.15232.

*4.2.5. (S,E)-1-tert-Butyl 2-methyl 3-(4-((tert-butyldiphenylsilyl)oxy) butylidene)-4-oxopyrrolidine-1,2-dicarboxylate (**10f**).* Obtained from the enaminone **9** (1.2 g, 4.04 mmol) using the general procedures. Purification of the residue by flash chromatography (hexanes/EtOAc=80/20) gave the title enone (1.44 g, 65%) as a thick colorless oil. $[\alpha]_D^{20}$ +19.9 (*c* 1.00, $CHCl_3$); IR (neat): ν_{max}=2934, 2859, 1747, 1710, 1428, 1393, 1255, 1160, 1109, 823, 740 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), mixture of rotamers: δ=7.68–7.63 (4H, m), 7.44–7.36 (6H, m), 6.87–6.82 (1H, m), 5.29–5.20 (1H, 2s), 4.08–3.93 (2H, m), 3.73–3.67 (5H, m), 2.63–2.40 (2H, m), 1.77–1.67 (2H, m), 1.50–1.46 (9H, 2s), 1.07–1.06 (9H, 2s); ^{13}C NMR (100 MHz, $CDCl_3$), mixture of rotamers: δ=197.1, 196.4, 170.4, 154.3, 153.5, 142.8, 142.6, 135.5, 133.5, 133.5, 129.6, 127.6, 81.2, 81.2, 63.0, 62.8, 60.2, 59.5, 53.3, 52.9, 52.5, 52.4, 30.9, 30.9, 28.2, 28.2, 26.8, 26.8, 26.5, 26.2, 19.1, 19.1; HRMS (ESIMS): calcd for $C_{23}H_{41}NO_4SiNa$ $[M+Na]^+$ 574.25954, found 574.25680.

*4.2.6. (S,E)-1-tert-Butyl 2-methyl 4-oxo-3-(3-phenylpropylidene) pyrrolidine-1,2-dicarboxylate (**10g**).* Obtained from the enaminone **9** (1.60 g, 5.37 mmol) using the general procedures. Purification of the residue by flash chromatography (hexanes/EtOAc=85/15) gave the title enone (1.04 g, 52%) as a thick colorless oil. $[\alpha]_D^{20}$ +70.5 (*c* 1.00, $CHCl_3$); IR (neat): ν_{max}=3034, 2982, 2937, 2360, 1745, 1703, 1655, 1607, 1499, 1481, 1457, 1439, 1395, 1370, 1322, 1258, 1204, 1161, 1122, 1025, 997, 917, 860, 773, 749, 701, 632 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), mixture of rotamers: δ=7.31–7.24 (2H, m), 7.24–7.16 (3H, m), 6.87–6.80 (1H, m), 5.24–5.08 (1H, 2s), 4.06–3.92 (2H, m), 3.71–3.70 (3H, 2s), 2.78–2.60 (4H, m), 1.49–1.46 (9H, 2s); ^{13}C NMR (100 MHz, $CDCl_3$), mixture of rotamers: δ=197.1, 196.4, 170.3, 154.3, 153.4, 141.6, 141.4, 140.2, 132.2, 131.9, 128.6, 128.6, 128.4, 128.4, 128.4, 128.3, 126.4, 81.3, 60.3, 59.6, 53.3, 52.9, 52.6, 52.5, 34.2, 31.4, 31.3, 28.3, 28.2; HRMS (ESIMS): calcd for $C_{20}H_{25}NO_5Na$ $[M+Na]^+$ 382.16249, found 382.16318.

*4.2.7. (S,E)-1-tert-Butyl 2-methyl 3-benzylidene-4-oxopyrrolidine-1,2-dicarboxylate (**10h**).* Obtained from the enaminone **9** (1.00 g, 3.35 mmol) using the general procedures. Purification of the residue by flash chromatography (hexanes/EtOAc=85/15) gave the title enone (685 mg, 62%) as a thick colorless oil. $[\alpha]_D^{20}$ +143.8 (*c*1.00, $CHCl_3$); IR (neat): ν_{max}=2985, 1747, 1707, 1629, 1601, 1498, 1480, 1454, 1438, 1396, 1371, 1320, 1259, 1210, 1162, 1124, 1055, 1015, 939, 911, 863, 763, 694, 632 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), mixture of rotamers: δ=7.82–7.78 (2H, m), 7.58 (1H, br s), 7.50–7.42 (3H, m), 5.77–5.61 (1H, 2s), 4.10–3.99 (2H, m), 3.66 (3H, br s), 1.50 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$), mixture of rotamers: δ=198.2, 197.5, 169.7, 169.5, 153.9, 153.1, 137.4, 137.2, 132.0, 131.3, 131.0, 128.6, 128.5, 128.4, 128.1, 127.9, 81.2, 81.1, 60.8, 60.1, 52.2, 52.2, 52.0, 51.6, 36.3, 27.9, 24.3; HRMS (ESIMS): calcd for $C_{18}H_{21}NO_5Na$ $[M+Na]^+$ 354.13119, found 354.13106.

*4.2.8. (S,E)-1-tert-Butyl 2-methyl 3-(4-methoxybenzylidene)-4-oxopyrrolidine-1,2-dicarboxylate (**10i**).* Obtained from the enaminone **9** (1.90 g, 6.37 mmol) using the general procedures. Purification of the residue by flash chromatography (hexanes/EtOAc=80/20) gave the title enone (1.35 g, 59%) as a thick colorless oil. $[\alpha]_D^{20}$ +130.0 (*c*1.00, $CHCl_3$); IR (neat): ν_{max}=2982, 2849, 1748, 1733, 1706, 1628, 1598, 1517, 1396, 1371, 1259, 1162, 1122, 1055, 1029, 769, 632 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), mixture of rotamers: δ=7.77 (2H, d, *J*=7.2 Hz), 7.48 (1H, d, *J*=4.4 Hz), 6.98–6.89 (2H, m), 5.69–5.55 (1H, 2s), 4.06–3.92 (2H, m), 3.83 (3H, s), 3.65 (3H, s), 1.47 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$), mixture of rotamers: δ=198.3, 197.7, 170.2, 170.0, 162.2, 154.2, 153.4, 137.5, 137.2, 133.9, 125.9, 125.6, 125.0, 114.4, 114.3, 81.3, 81.2, 61.3, 60.5, 55.3, 53.3, 52.4, 52.4, 52.3, 51.9, 28.2; HRMS (ESIMS): calcd for $C_{19}H_{23}NO_6Na$ $[M+Na]^+$ 384.14176, found 384.14056.

*4.2.9. (S,E)-1-tert-Butyl 2-methyl 3-(4-fluorobenzylidene)-4-oxopyrrolidine-1,2-dicarboxylate (**10j**).* Obtained from the enaminone **9** (1.20 g, 4.04 mmol) using the general procedures. Purification of the residue by flash chromatography (hexanes/EtOAc=80/20) gave the title enone (825 mg, 59%) as a thick colorless oil. $[\alpha]_D^{20}$ +238.4 (*c* 1.00, $CHCl_3$); IR (neat): ν_{max}=2985, 1742, 1703, 1630, 1602, 1514, 1482, 1438, 1395, 1371, 1329, 1301, 1238, 1160, 1125, 1053, 1015, 914, 862, 834, 786, 775, 736, 632 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), mixture of rotamers: δ=7.86 (2H, t, *J*=7.2 Hz), 7.54 (1H, d, *J*=4.4 Hz), 7.21–7.11 (2H, m), 5.73–5.58 (1H, 2s), 4.06–3.99 (2H, m), 3.68 (3H, br s), 1.51 (9H, s). ^{13}C NMR (100 MHz, $CDCl_3$), mixture of rotamers: δ=198.0, 197.4, 169.6, 169.5, 165.3, 162.7, 153.9, 153.0, 136.1, 135.8, 133.6, 133.5, 127.9, 127.6, 115.9, 115.8, 114.6, 114.4, 81.3, 81.1, 60.8, 60.0, 52.3, 52.3, 52.0, 51.6, 27.9; HRMS (ESIMS): calcd for $C_{18}H_{20}NFO_5Na$ $[M+Na]^+$ 372.12177, found 372.12254.

4.3. Typical procedure for synthesis of allylic alcohols (11a–j)

Under argon and in a flame-dried flask, the starting enone (1 equiv) was dissolved in dry THF (0.2 M) and commercial solution of $LaCl_3\cdot 2LiCl$ (0.6 in THF, 1.05 equiv) was added at rt. The mixture was allowed to stir as such for 1 h, then it was cooled to −78 °C and MeMgBr (3.0 M in Et_2O, 1.5 equiv) was added dropwise. The resulting brownish solution was stirred at −78 °C for 1 h, then quenched at −78 °C with aqueous saturated NH_4Cl. The biphasic mixture was separated and the aqueous phase was extracted three times with Et_2O. Special care was taken to avoid acidic wash (no 1 M HCl), as analogous intermediates were shown to decompose rapidly under such conditions. The combined organic layers were washed with brine and dried over Na_2SO_4, and the solvent was removed under reduced pressure.

*4.3.1. (2S,4S,E)-1-tert-Butyl 2-methyl 3-ethylidene-4-hydroxy-4-methylpyrrolidine-1,2-dicarboxylate (**11a**) and (2S,4R,E)-1-tert-butyl 2-methyl 3-ethylidene-4-hydroxy-4-methylpyrrolidine-1,2-dicarboxylate (**12**).* Obtained from the enone **10a** (1.00 g, 3.72 mmol) using the general procedures. Purification of the

residue by flash chromatography (hexanes/EtOAc=70/30) gave the title allylic alcohol (785 mg, 74%) as a thick yellowish oil. **Compound 11a**: $[\alpha]_D^{20}$ +67.8 (*c* 1.00, $CHCl_3$); IR (neat): ν_{max}=3464, 2969, 2928, 1707, 1398, 1367, 1259, 1170, 1140, 1116, 990, 899, 769 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), mixture of rotamers: δ=5.82–5.77 (1H, qd, *J*=7.0, 1.7 Hz), 4.93–4.86 (1H, 2s), 4.13–3.90 (1H, 2s), 3.84–3.73 (1H, m), 3.82–3.79 (3H, 2s), 3.31–3.26 (1H, m), 1.78–1.76 (3H, 2s), 1.46–1.44 (9H, 2s), 1.41–1.40 (3H, 2s); ^{13}C NMR (100 MHz, $CDCl_3$), mixture of rotamers: δ=173.5, 173.1, 154.1, 139.6, 138.9, 128.4, 125.9, 121.8, 80.3, 76.3, 76.1, 75.2, 60.5, 60.3, 60.3, 60.0, 59.6, 52.6, 52.3, 29.6, 29.3, 28.0, 27.9, 20.7, 20.5, 14.0, 13.9; HRMS (ESIMS): calcd for $C_{14}H_{23}NO_5Na$ $[M+Na]^+$ 308.14684, found 308.14627. **Compound 12**: $[\alpha]_D^{20}$ +78.8 (*c* 1.00, $CHCl_3$); IR (neat): ν_{max}=3432, 2976, 1747, 1683, 398, 1167, 1133, 999, 774 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), mixture of rotamers: δ=5.90–5.85 (1H, m), 5.09–4.99 (1H, 2s), 3.77–3.68 (1H, m), 3.75–3.74 (3H, 2s), 3.49–3.46 (1H, 2s), 2.08 (1H, br s), 1.82–1.80 (3H, 2s), 1.48–1.44 (12H, 2s); ^{13}C NMR (100 MHz, $CDCl_3$), mixture of rotamers: δ=171.0, 154.6, 153.7, 142.6, 142.2, 122.0, 121.9, 80.5, 80.4, 76.1, 61.1, 60.6, 59.9, 59.3, 52.1, 52.0, 28.3, 28.2, 27.3, 27.2, 14.5, 14.4; HRMS (ESIMS): calcd for $C_{14}H_{23}NO_5Na$ $[M+Na]^+$ 308.14684, found 308.14747.

*4.3.2. (2S,4S,E)-1-tert-Butyl 2-methyl 3-(cyclopentylmethylene)-4-hydroxy-4-methylpyrrolidine-1,2-dicarboxylate (**11b**).* Obtained from the enone **10b** (770 mg, 2.38 mmol) using the general procedures. Purification of the residue by flash chromatography (hexanes/EtOAc=70/30) gave the title allylic alcohol (635 mg, 78%) as a thick yellowish oil. $[\alpha]_D^{20}$ +103.5 (*c* 1.00, $CHCl_3$); IR (neat): ν_{max}=3473, 2952, 2869, 1703, 1396, 1340, 1253, 1209, 1159, 1113, 998, 929, 907, 881 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), mixture of rotamers: δ=5.57–5.54 (1H, 2s), 4.90–4.83 (1H, 2s), 3.76–3.74 (3H, 2s), 3.70–3.67 (1H, 2s), 3.25–3.23 (1H, 2s), 2.73–2.66 (1H, m), 1.83–1.73 (1H, m), 1.67–1.53 (4H, m), 1.41–1.38 (9H, 2s), 1.36–1.35 (3H, m) 1.22–1.15 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$), mixture of rotamers: δ=174.1, 173.8, 154.5, 153.5, 137.3, 136.6, 132.5, 132.5, 80.6, 80.5, 76.4, 75.5, 65.8, 60.9, 60.7, 60.6, 59.9, 53.1, 52.8, 39.7, 33.3, 32.8, 28.3, 28.2, 25.5, 25.5, 25.4, 21.3, 21.1, 15.2; HRMS (ESIMS): calcd for $C_{18}H_{29}NO_5Na$ $[M+Na]^+$ 362.19379, found 362.19431.

*4.3.3. (2S,4S,E)-1-tert-Butyl 2-methyl 4-hydroxy-4-methyl-3-undecylidenepyrrolidine-1,2-dicarboxylate (**11c**).* Obtained from the enone **10c** (415 mg, 1.05 mmol) using the general procedures. Purification of the residue by flash chromatography (hexanes/EtOAc=80/20) gave the title allylic alcohol (265 mg, 62%) as a thick yellowish oil. $[\alpha]_D^{20}$ +99.1 (*c* 1.00, $CHCl_3$); IR (neat): ν_{max}=3480, 2932, 2862, 1736, 1711, 1398, 1371, 1259, 1217, 1173, 997, 907, 768 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), mixture of rotamers: δ=5.72 (1H, t, *J*=7.7 Hz), 4.91–4.83 (1H, 2s), 3.84–3.74 (1H, m), 3.81–3.78 (3H, 2s), 3.30–3.27 (1H, 2s), 2.19–2.10 (2H, m), 1.47–1.44 (9H, 2s), 1.42–1.41 (3H, 2s), 1.43–1.25 (16H, m), 0.89 (3H, t, *J*=6.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$), mixture of rotamers: δ=174.1, 173.7, 154.5, 153.5, 138.8, 138.1, 127.9, 127.8, 80.7, 80.6, 76.5, 75.6, 61.0, 60.8, 60.7, 60.0, 53.0, 52.6, 31.9, 29.6, 29.6, 29.5, 29.3, 29.3, 29.0, 29.0, 28.3, 28.3, 22.7, 21.2, 21.0, 14.1; HRMS (ESIMS): calcd for $C_{23}H_{41}NO_5Na$ $[M+Na]^+$ 434.28769, found 434.28790.

*4.3.4. (2S,4S,E)-1-tert-Butyl 2-methyl 3-(3-(1,3-dioxolan-2-yl)propylidene)-4-hydroxy-4-methylpyrrolidine-1,2-dicarboxylate (**11d**).* Obtained from the enone **10d** (500 mg, 1.41 mmol) using the general procedures. Purification of the residue by flash chromatography (hexanes/EtOAc=70/30) gave the title allylic alcohol (375 mg, 72%) as a thick yellowish oil. $[\alpha]_D^{20}$ +75.4 (*c* 1.00, $CHCl_3$); IR (neat): ν_{max}=3464, 2978, 2876, 1747, 1704, 1396, 1161, 1020, 937, 898, 854, 767 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), mixture of rotamers: δ=5.68–5.64 (1H, m), 4.93–4.82 (2H, m), 3.97–3.94 (2H, m), 3.87–3.82 (2H, m), 3.72–3.70 (3H, 2s), 3.72–3.66 (1H, m), 3.20 (1H, d, *J*=11.2 Hz), 2.33–2.22 (2H, m), 1.78–1.68 (2H, m), 1.38–1.35 (9H, 2s), 1.38–1.30 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$), mixture of rotamers: δ=173.6, 173.3, 154.3, 153.3, 139.3, 138.6, 126.4, 103.6, 103.5, 80.4, 80.4, 80.2, 76.3, 75.4, 64.8, 64.7, 60.7, 60.5, 60.4, 59.7, 52.8, 52.5, 32.8, 32.7, 28.1, 28.1, 23.2, 21.2, 21.0; HRMS (ESIMS): calcd for $C_{18}H_{29}NO_7Na$ $[M+Na]^+$ 394.18412, found 394.18362.

*4.3.5. (2S,4S,E)-1-tert-Butyl 2-methyl 3-(4-((tert-butyldiphenylsilyl)oxy)butylidene)-4-hydroxy-4-methylpyrrolidine-1,2-dicarboxylate (**11f**).* Obtained from the enone **10f** (500 mg, 0.907 mmol) using the general procedures. Purification of the residue by flash chromatography (hexanes/EtOAc=80/20) gave the title allylic alcohol (325 mg, 63%) as a thick yellowish oil. $[\alpha]_D^{20}$ +63.2 (*c* 1.00, $CHCl_3$); IR (neat): ν_{max}=3474, 2933, 2861, 1705, 1395, 1162, 1107, 1001, 821, 739, 704 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), mixture of rotamers: δ=7.71–7.66 (4H, m), 7.47–7.36 (6H, m), 5.75–5.68 (1H, m), 4.93–4.89 (1H, 2s), 4.18–3.97 (1H, 2s), 3.87–3.76 (1H, m), 3.77–3.76 (3H, 2s), 3.74–3.65 (2H, m), 3.29–3.26 (1H, 2s), 2.46–2.16 (2H, m), 1.73–1.61 (2H, m), 1.49–1.44 (9H, s), 1.40–1.39 (3H, 2s), 1.09–1.07 (9H, 2s); ^{13}C NMR (100 MHz, $CDCl_3$), mixture of rotamers: δ=173.7, 173.4, 154.1, 153.1, 139.0, 138.2, 135.2, 135.1, 133.4, 129.3, 127.3, 126.8, 80.3, 80.3, 76.1, 75.2, 62.8, 62.5, 60.5, 60.3, 59.6, 52.6, 52.3, 31.4, 31.3, 28.0, 27.9, 26.5, 26.5, 25.1, 24.9, 20.7, 18.9; HRMS (ESIMS): calcd for $C_{32}H_{45}NO_6SiNa$ $[M+Na]^+$ 590.29084, found 590.29197.

*4.3.6. (2S,4S,E)-1-tert-Butyl 2-methyl 4-hydroxy-4-methyl-3-(3-phenylpropylidene)pyrrolidine-1,2-dicarboxylate (**11g**).* Obtained from the enone **10g** (500 mg, 1.33 mmol) using the general procedures. Purification of the residue by flash chromatography (hexanes/EtOAc=70/30) gave the title allylic alcohol (477 mg, 91%) as a thick yellowish oil. $[\alpha]_D^{20}$ +72.4 (*c* 1.00, $CHCl_3$); IR (neat): ν_{max}=3454, 3034, 2983, 2936, 1735, 1703, 1607, 1500, 1481, 1457, 1395, 1370, 1258, 1205, 1155, 1116, 996, 974, 933, 907, 861, 819, 773, 750, 701, 627 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), mixture of rotamers: δ=7.32–7.25 (2H, m), 7.25–7.20 (3H, m), 5.77 (1H, t, *J*=7.7 Hz), 4.83–4.69 (1H, 2s), 4.14–3.89 (1H, 2s), 3.79–3.76 (3H, 2s), 3.80–3.72 (1H, m), 3.26–3.23 (1H, 2s), 2.74–2.65 (2H, m), 2.52–2.44 (2H, m), 1.48–1.44 (9H, 2s), 1.45–1.41 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$), mixture of rotamers: δ=173.9, 173.4, 171.0, 154.5, 153.5, 141.3, 141.0, 139.8, 139.0, 128.4, 126.5, 126.3, 126.2, 126.1, 126.1, 80.7, 80.7, 76.5, 75.7, 60.9, 60.7, 60.5, 59.8, 53.1, 52.7, 35.2, 35.2, 35.1, 30.7, 30.7, 28.3, 28.3, 21.3, 21.1; HRMS (ESIMS): calcd for $C_{21}H_{29}NO_5Na$ $[M+Na]^+$ 398.19379, found 398.19474.

*4.3.7. (2S,4S,E)-1-tert-Butyl 2-methyl 3-benzylidene-4-hydroxy-4-methylpyrrolidine-1,2-dicarboxylate (**11h**).* Obtained from the enone **10h** (475 mg, 1.44 mmol) using the general procedures. Purification of the residue by flash chromatography (hexanes/EtOAc=80/20) gave the title allylic alcohol (443 mg, 89%) as a thick yellowish oil. $[\alpha]_D^{20}$ +234.9 (*c* 1.00, $CHCl_3$); IR (neat): ν_{max}=3430, 2984, 2253, 1694, 1481, 1451, 1396, 1370, 1257, 1214, 1160, 1116, 1083, 1002, 912, 860, 818, 733, 698, 649, 633 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), mixture of rotamers: δ=7.50–7.26 (5H, m), 6.75 (1H, br s), 5.26–5.13 (1H, 2s), 4.57–4.32 (1H, 2s), 3.77–3.73 (1H, m), 3.72–3.70 (3H, 2s), 3.40–3.36 (1H, dd, *J*=11.2, 4.4 Hz), 1.56 (3H, s), 1.47–1.44 (9H, 2s); ^{13}C NMR (100 MHz, $CDCl_3$), mixture of rotamers: δ=173.5, 173.0, 154.0, 153.0, 139.3, 138.4, 134.7, 134.5, 134.4, 128.5, 128.4, 128.1, 127.9, 127.8, 127.8, 127.5, 126.5, 126.4, 80.5, 80.4, 77.2, 76.3, 60.8, 60.7, 59.5, 58.9, 52.7, 52.3, 28.0, 27.9, 26.7, 21.8, 21.5; HRMS (ESIMS): calcd for $C_{19}H_{25}NO_5Na$ $[M+Na]^+$ 370.16249, found 370.16292.

*4.3.8. (2S,4S,E)-1-tert-Butyl 2-methyl 4-hydroxy-3-(4-methoxy benzylidene)-4-methylpyrrolidine-1,2-dicarboxylate (**11i**).* Obtained from the enone **10i** (500 mg, 1.39 mmol) using the general

procedures. Purification of the residue by flash chromatography (hexanes/EtOAc=70/30) gave the title allylic alcohol and its minor diastereomer in an inseparable mixture (385 mg, 74%, dr=3:1) as a thick yellowish oil. $[\alpha]_D^{20}$ +192.6 (*c* 1.00, $CHCl_3$); IR (neat): ν_{max}=3437, 2983, 2845, 2256, 1694, 1610, 1516, 1459, 1397, 1370, 1304, 1254, 1217, 1161, 1138, 1114, 1071, 1035, 911, 831, 731, 649, 633 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), mixture of rotamers: δ=7.48–7.40 (2H, m), 6.94–6.84 (2H, m), 6.65 (1H, br s), 5.25–5.12 (1H, 2s), 4.54–4.30 (1H, 2s), 3.82–3.81 (3H, 2s), 3.75–3.72 (3H, 2br s), 3.30 (1H, dd, *J*=11.3, 3.9 Hz), 1.53 (3H, s), 1.45–1.43 (9H, 2s); ^{13}C NMR (100 MHz, $CDCl_3$), mixture of rotamers: δ=173.8, 173.4, 159.6, 159.3, 154.3, 153.4, 137.1, 136.2, 130.5, 127.3, 126.4, 113.9, 80.8, 80.7, 77.8, 61.3, 61.1, 59.9, 59.2, 55.2, 55.2, 53.1, 52.7, 28.3, 22.2, 22.0; HRMS (ESIMS): calcd for $C_{20}H_{27}NO_6Na$ $[M+Na]^+$ 400.17306, found 400.17332.

*4.3.9. (2S,4S,E)-1-tert-Butyl 2-methyl 3-(4-fluorobenzylidene)-4-hydroxy-4-methylpyrrolidine-1,2-dicarboxylate (**11j**).* Obtained from the enone **10j** (500 mg, 1.43 mmol) using the general procedures. Purification of the residue by flash chromatography (hexanes/EtOAc=70/30) gave the title allylic alcohol (416 mg, 80%) as a thick yellowish oil. $[\alpha]_D^{20}$ +174.6 (*c* 1.00, $CHCl_3$); IR (neat): ν_{max}=3440, 2983, 2350, 2256, 1697, 1607, 1513, 1491, 1458, 1396, 1370, 1225, 1160, 1116, 1072, 1014, 910, 859, 837, 820, 774, 732, 648 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), mixture of rotamers: δ=7.49–7.40 (2H, m), 7.09–7.02 (2H, m), 6.68 (1H, br s), 5.21–5.08 (1H, 2s), 4.44–4.21 (1H, 2s), 3.84–3.74 (1H, m), 3.71–3.69 (3H, 2s), 3.39–3.33 (1H, 2br s), 1.54 (3H, s), 1.46–1.42 (9H, 2s); ^{13}C NMR (100 MHz, $CDCl_3$), mixture of rotamers: δ=173.5, 173.0, 163.7, 161.2, 154.3, 153.3, 139.6, 138.7, 131.0, 130.7, 130.6, 125.7, 125.6, 115.6, 115.4, 115.1, 80.9, 80.8, 61.1, 61.0, 59.8, 59.1, 53.1, 52.7, 28.3, 22.2, 22.0; HRMS (ESIMS): calcd for $C_{19}H_{24}NFO_5Na$ $[M+Na]^+$ 388.15307, found 388.15441.

4.4. Typical procedure for synthesis of trisubstituted 3-pyrrolines 13a–j

Method A: the starting allylic alcohol (1 equiv) was dissolved in EtOAc (0.2 M) and $Pd(OH)_2$ (10 mol %) was added. The resulting mixture was purged with hydrogen and stirred for 16 h under hydrogen atmosphere. The mixture was filtered over Celite and the solvent was removed under reduced pressure. *Method B*: a solution of the starting allylic alcohol (1 equiv) in MeOH (0.2 M) was added Pd/C (1 mol %), then Et_3SiH (2 equiv). The reaction mixture was stirred at rt for variable times, after which it was filtered through Celite and the solvent was removed under reduced pressure.

*4.4.1. (S)-1-tert-Butyl 2-methyl 3-ethyl-4-methyl-1H-pyrrole-1,2(2H,5H)-dicarboxylate (**13a**), (2S,4S,Z)-1-tert-butyl 2-methyl 3-ethylidene-4-methylpyrrolidine-1,2-dicarboxylate (**14**) and (2S,3S,4S)-1-tert-butyl 2-methyl 3-ethyl-4-hydroxy-4-methylpyrrolidine-1,2-dicarboxylate (**15**).* Obtained from the allylic alcohol **11a** (200 mg, 0.701 mmol) using the general procedures. Purification of the residue by flash chromatography (hexanes/EtOAc=80/20) gave the title pyrroline **13a** (120 mg, 63%, method A—Table 1, entry 3), the regioisomer **14** (19 mg, 10%) and the hydrogenated product **15** (20 mg, 10%) as colorless oils. **Compound 13a**: $[\alpha]_D^{20}$ −141.8 (*c* 1.00, $CHCl_3$); IR (neat): ν_{max}=2968, 2922, 1759, 1706, 1400, 1244, 1163, 1117, 1003, 906, 772 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), mixture of rotamers: δ=4.94–4.86 (1H, 2br s), 4.20–4.11 (1H, m), 4.10–4.01 (1H, m), 3.75–3.73 (3H, 2s), 2.25–2.17 (1H, m), 1.97–1.86 (1H, m), 1.70–1.68 (3H, 2s), 1.47–1.43 (9H, 2s), 1.01 (3H, t, *J*=7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$), mixture of rotamers: δ=171.5, 171.4, 153.4, 152.9, 130.8, 130.6, 129.9, 129.8, 79.6, 79.5, 67.9, 67.4, 56.9, 56.6, 51.6, 51.5, 28.0, 27.9, 18.1, 12.2, 12.1, 11.0, 11.0; HRMS (ESIMS): calcd for $C_{14}H_{23}NO_4Na$ $[M+Na]^+$ 292.15110, found 292.15193. **Compound 14**: ^1H NMR (400 MHz, $CDCl_3$), mixture of rotamers: δ=5.47–5.42 (1H, m), 4.87–4.76 (1H, 2s), 3.66–3.65 (3H, 2s), 3.64–3.58 (1H, m), 3.24–3.16 (1H, m), 2.79–2.58 (1H, m), 1.69–1.66 (3H, 2s), 1.40–1.36 (9H, 2s), 1.12–1.07 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$), mixture of rotamers: δ=171.6, 171.4, 154.3, 153.6, 140.8, 140.1, 122.1, 120.6, 120.5, 79.7, 79.6, 60.9, 60.4, 52.7, 52.2, 51.7, 51.5, 37.7, 36.9, 28.0, 27.9, 27.4, 20.2, 14.4, 14.3. **Compound 15**: $[\alpha]_D^{20}$ −2.4 (*c* 1.00, $CHCl_3$); IR (neat): ν_{max}=3455, 2928, 1701, 1393, 1367, 1214, 1156, 1106, 1029, 899, 767 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), mixture of rotamers: δ=4.94–4.44 (1H, 2d, *J*=9.1 Hz), 4.19–3.94 (1H, 2s), 3.80–3.78 (3H, s), 3.76–3.64 (1H, m), 3.37–3.32 (1H, m), 2.10–2.05 (1H, m), 1.44–1.40 (9H, 2s), 1.28–1.27 (3H, 2s), 1.27–1.18 (1H, m), 1.02 (3H, t, *J*=7.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$), mixture of rotamers: δ=175.3, 175.0, 154.0, 153.1, 80.0, 80.0, 77.5, 62.4, 62.1, 60.8, 60.2, 60.0, 53.0, 52.2, 52.1, 51.9, 29.3, 27.9, 27.9, 22.2, 17.0, 16.9, 12.4; HRMS (ESIMS): calcd for $C_{14}H_{25}NO_5Na$ $[M+Na]^+$ 310.16304, found 310.16074.

*4.4.2. (S)-1-tert-Butyl 2-methyl 3-(1-d-ethyl)-4-methyl-1H-pyrrole-1,2(2H,5H)-dicarboxylate (**16**) and (2S,4S,Z)-1-tert-butyl 2-methyl 3-ethylidene-4-d-4-methylpyrrolidine-1,2-dicarboxylate (**17**).* Obtained from the allylic alcohol **11a** (100 mg, 0.351 mmol) using method A with D_2 gas. Purification of the residue by flash chromatography (hexanes/EtOAc=80/20) gave the pyrroline **16** (60 mg, 63%) and pyrrolidine **17** (9.5 mg, 10%) as a thick yellowish oil. **Compound 16**: ^1H NMR (400 MHz, $CDCl_3$), mixture of rotamers: δ=4.94–4.86 (1H, 2br s), 4.20–4.11 (1H, m), 4.10–4.01 (1H, m), 3.75–3.73 (3H, 2s), 1.97–1.86 (1H, m), 1.70–1.68 (3H, 2s), 1.47–1.43 (9H, 2s), 1.01 (3H, t, *J*=7.6 Hz); HRMS (ESIMS): calcd for $C_{14}H_{22}NDO_4Na$ $[M+Na]^+$ 293.15821, found 293.15779. **Compound 17**: ^1H NMR (400 MHz, $CDCl_3$), mixture of rotamers: δ=5.47–5.42 (1H, m), 4.87–4.76 (1H, 2s), 3.66–3.65 (3H, 2s), 3.64–3.58 (1H, m), 3.24–3.16 (1H, m), 1.69–1.66 (3H, 2s), 1.40–1.36 (9H, 2s), 1.12–1.07 (3H, m); HRMS (ESIMS): calcd for $C_{14}H_{22}NDO_4Na$ $[M+Na]^+$ 293.15821, found 293.15779.

*4.4.3. (S)-1-tert-Butyl 2-methyl 3-(cyclopentylmethyl)-4-methyl-1H-pyrrole-1,2(2H,5H)-dicarboxylate (**13b**).* Obtained from the allylic alcohol **11b** (225 mg, 0.663 mmol) using the general procedures. Purification of the residue by flash chromatography (hexanes/EtOAc=80/20) gave the title pyrroline (155 mg, 73%, method A) as a thick yellowish oil. $[\alpha]_D^{20}$ −158.3 (*c* 1.00, $CHCl_3$); IR (neat): ν_{max}=2949, 2870, 1749, 1703, 1684, 1446, 1397, 1365, 1241, 1169, 1117, 1016 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), mixture of rotamers: δ=4.95–4.87 (1H, 2s), 4.25–4.123 (1H, m), 4.11–4.01 (1H, m), 3.75–3.73 (3H, 2s), 2.15–1.94 (3H, m), 1.83–1.75 (1H, m), 1.72–1.70 (3H, 2s), 1.68–1.52 (5H, m), 1.49–1.44 (9H, 2s), 1.27–1.13 (1H, m), 1.08–1.03 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$), mixture of rotamers: δ=172.2, 172.6, 154.7, 154.1, 131.9, 131.9, 130.5, 130.3, 80.8, 69.6, 69.2, 58.1, 57.8, 52.8, 52.7, 39.4, 33.8, 33.8, 32.8, 32.1, 29.3, 29.1, 25.8, 25.6, 12.6, 12.6; HRMS (ESIMS): calcd for $C_{18}H_{29}NO_4Na$ $[M+Na]^+$ 346.19888, found 346.19805.

*4.4.4. (S)-1-tert-Butyl 2-methyl 3-undecyl-4-methyl-1H-pyrrole-1,2(2H,5H)-dicarboxylate (**13c**).* Obtained from the allylic alcohol **11c** (100 mg, 0.243 mmol) using the general procedures. Purification of the residue by flash chromatography (hexanes/EtOAc=90/10) gave the title pyrroline (65 mg, 68%, method A) as a thick yellowish oil. $[\alpha]_D^{20}$ −80.7 (*c* 1.00, $CHCl_3$); IR (neat): ν_{max}=2924, 2855, 1748, 1709, 1457, 1397, 1245, 1169, 1119, 1012, 910, 859, 772, 730 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), mixture of rotamers: δ=4.89–4.81 (1H, 2br s), 4.20–4.12 (1H, dt, *J*=13.8, 4.3 Hz), 4.08–3.98 (1H, m), 3.73–3.71 (3H, 2s), 2.21–2.10 (1H, m), 1.96–1.85 (1H, m), 1.69–1.66 (3H, 2s), 1.46–1.42 (9H, 2s), 1.34–1.20 (18H, m), 0.90–0.85 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$), mixture of rotamers: δ=171.9, 171.8, 153.8, 153.3, 130.8, 129.7, 129.7, 80.0, 68.6, 68.1,

57.3, 57.0, 52.0, 51.8, 31.9, 29.6, 29.6, 29.6, 29.4, 29.3, 28.4, 28.3, 27.8, 25.3, 22.7, 14.1, 11.6, 11.5; HRMS (ESIMS): calcd for $C_{23}H_{41}NO_4Na$ $[M+Na]^+$ 418.29278, found 418.29227.

*4.4.5. (S)-1-tert-Butyl 2-methyl 3-(3-(1,3-dioxolan-2-yl)propyl)-4-methyl-1H-pyrrole-1,2(2H,5H)-dicarboxylate (**13d**).* Obtained from the allylic alcohol **11d** (100 mg, 0.269 mmol) using the general procedures. Purification of the residue by flash chromatography (hexanes/EtOAc=80/20) gave the title pyrroline (74 mg, 78%, method A) as a thick yellowish oil. $[\alpha]_D^{20}$ +75.8 (*c* 1.00, $CHCl_3$); IR (neat): ν_{max}=3473, 2952, 1747, 1710, 1402, 1367, 1247, 1172, 1121, 1032, 939, 772 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), mixture of rotamers: δ=4.87–4.81 (1H, m), 4.19–4.12 (1H, m), 4.11–4.05 (1H, 2s), 3.98–3.91 (2H, m), 3.88–3.81 (2H, m), 3.73–3.70 (3H, 2s), 2.24–2.16 (1H, m), 2.03–1.95 (1H, m), 1.74–1.59 (7H, m), 1.46–1.41 (10H, s); ^{13}C NMR (100 MHz, $CDCl_3$), mixture of rotamers: δ=171.8, 171.6, 153.8, 153.2, 131.6, 129.2, 129.1, 104.3, 80.0, 79.9, 76.9, 68.4, 68.0, 64.9, 57.3, 57.0, 52.0, 51.9, 33.4, 33.3, 28.4, 28.3, 25.0, 22.1, 22.0, 11.6, 11.6; HRMS (ESIMS): calcd for $C_{18}H_{29}NO_6Na$ $[M+Na]^+$ 378.18903, found 378.18871.

*4.4.6. (S)-1-tert-Butyl 2-methyl 3-(4-((tert-butyldiphenylsilyl)oxy)butyl)-4-methyl-1H-pyrrole-1,2(2H,5H)-dicarboxylate (**13f**).* Obtained from the allylic alcohol **11f** (200 mg, 0.353 mmol) using the general procedures. Purification of the residue by flash chromatography (hexanes/EtOAc=90/10) gave the title pyrroline (135 mg, 70%, method A) as a thick yellowish oil. $[\alpha]_D^{20}$ −58.6 (*c* 1.00, $CHCl_3$); IR (neat): ν_{max}=2934, 2859, 1748, 1708, 1397, 1246, 1173, 1111, 1008 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), mixture of rotamers: δ=7.69–7.64 (4H, m), 7.44–7.36 (6H, m), 4.88–4.82 (1H, 2s), 4.23–4.13 (1H, m), 4.10–3.96 (1H, m), 3.71–3.69 (3H, 2s), 3.68–3.62 (2H, m), 2.20–2.13 (1H, m), 1.93–1.87 (1H, m), 1.66–1.64 (3H, 2s), 1.58–1.49 (4H, m), 1.48–1.42 (9H, s), 1.05 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$), mixture of rotamers: δ=171.8, 171.7, 153.7, 153.2, 135.5, 134.0, 131.2, 129.5, 129.4, 127.6, 80.0, 79.9, 68.4, 68.0, 63.5, 57.2, 56.9, 52.0, 51.8, 32.2, 32.1, 28.4, 28.3, 26.8, 25.0, 25.0, 24.0, 23.9, 19.2, 11.6, 11.5; HRMS (ESIMS): calcd for $C_{32}H_{45}NO_5SiNa$ $[M+Na]^+$ 574.29592, found 574.29731.

*4.4.7. (S)-1-tert-Butyl 2-methyl 4-methyl-3-(3-phenylpropyl)-1H-pyrrole-1,2(2H,5H)-dicarboxylate (**13g**).* Obtained from the allylic alcohol **11g** (100 mg, 0.267 mmol) using the general procedures. Purification of the residue by flash chromatography (hexanes/EtOAc=80/20) gave the title pyrroline (48 mg, 50%, method B) as a thick yellowish oil. $[\alpha]_D^{20}$ −93.6 (*c* 1.00, $CHCl_3$); IR (neat): ν_{max}=2977, 2934, 2855, 1748, 1707, 1398, 1247, 1172, 1119, 1011, 908, 745, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), mixture of rotamers: δ=7.32–7.28 (2H, m), 7.24–7.18 (3H, m), 4.95–4.86 (1H, 2s), 4.24–4.16 (1H, m), 4.11–4.01 (1H, q, *J*=15.3 Hz), 3.72–3.71 (3H, br s), 2.68–2.57 (2H, m), 2.28–2.19 (1H, m), 2.03–1.93 (1H, m), 1.92–1.82 (1H, m), 1.75–1.64 (4H, m), 1.50–1.45 (9H, 2s); ^{13}C NMR (100 MHz, $CDCl_3$), mixture of rotamers: δ=171.8, 171.7, 153.8, 153.2, 141.8, 131.4, 129.4, 129.2, 128.3, 128.3, 125.8, 80.0, 68.5, 68.0, 57.3, 56.9, 52.0, 51.9, 35.5, 35.4, 29.2, 29.1, 28.4, 28.3, 24.9, 24.9, 11.7, 11.6; HRMS (ESIMS): calcd for $C_{21}H_{29}NO_4$ $[M+H]^+$ 382.19888, found 382.20035.

*4.4.8. (S)-1-tert-Butyl 2-methyl 3-benzyl-4-methyl-1H-pyrrole-1,2(2H,5H)-dicarboxylate (**13h**).* Obtained from the allylic alcohol **11h** (100 mg, 0.288 mmol) using the general procedures. Purification of the residue by flash chromatography (hexanes/EtOAc=80/20) gave the title pyrroline (45 mg, 47%, method B) as a thick yellowish oil. $[\alpha]_D^{20}$ −56.7 (*c* 1.00, $CHCl_3$); IR (neat): ν_{max}=2974, 2925, 2856, 1746, 1702, 1448, 1393, 1246, 1170, 1115, 1013, 904, 860, 769, 700, 560 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), mixture of rotamers: δ=7.30–7.14 (5H, m), 4.80–4.72 (1H, 2br s), 4.27–4.22 (1H, m), 4.09–4.04 (1H, m), 3.56 (3H, br s), 3.34–3.28 (1H, m), 2.99–2.87 (1H, m), 1.47 (3H, br s), 1.42–1.39 (9H, 2s); ^{13}C NMR (100 MHz, $CDCl_3$), mixture of rotamers: δ=172.3, 171.5, 153.2, 139.7, 139.5, 138.2, 132.6, 132.5, 128.7, 128.5, 128.4, 128.3, 126.4, 126.3, 80.1, 68.4, 68.0, 62.2, 61.9, 57.3, 57.0, 53.8, 53.2, 51.9, 51.7, 46.1, 45.3, 34.5, 33.7, 31.8, 31.5, 28.4, 28.3, 11.9, 11.8; HRMS (ESIMS): calcd for $C_{19}H_{25}NO_4Na$ $[M+Na]^+$ 354.16758, found 354.16756.

*4.4.9. (S)-1-tert-Butyl 2-methyl 3-(4-methoxybenzyl)-4-methyl-1H-pyrrole-1,2(2H,5H)-dicarboxylate (**13i**).* Obtained from the allylic alcohol **11i** (100 mg, 0.265 mmol) using the general procedures. Purification of the residue by flash chromatography (hexanes/EtOAc=80/20) gave the title pyrroline (59 mg, 62%, method B) as a thick yellowish oil. $[\alpha]_D^{20}$ −19.4 (*c* 1.00, $CHCl_3$); IR (neat): ν_{max}=2976, 2937, 1747, 1699, 1611, 1512, 1453, 1394, 1296, 1246, 1174, 1146, 1114, 1033, 989, 903, 818, 772, 738 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), mixture of rotamers: δ=7.16–7.10 (2H, m), 6.88–6.82 (2H, m), 4.40–4.32 (1H, 2d, *J*=8.7 Hz), 3.80 (3H, s), 3.70–3.68 (3H, 2s), 2.52–2.40 (2H, m), 2.91–2.83 (2H, m), 1.47 (3H, br s), 1.41–1.39 (9H, 2s); ^{13}C NMR (100 MHz, $CDCl_3$), mixture of rotamers: δ=172.4, 172.1, 158.0, 154.6, 154.0, 131.6, 129.6, 129.4, 128.7, 113.9, 113.8, 79.9, 79.8, 68.4, 68.0, 62.1, 61.8, 57.3, 57.0, 55.2, 53.7, 53.2, 51.9, 51.7, 46.4, 45.5, 34.5, 33.7, 30.9, 28.4, 28.3, 14.5, 14.3; HRMS (ESIMS): calcd for $C_{20}H_{27}NO_5Na$ $[M+Na]^+$ 384.17814, found 384.17890.

4.5. Typical procedure for synthesis of 3,4-disubstituted L-prolines (16a–d, g–j)

A solution of starting trisubstituted pyrrolines (1 equiv) in EtOAc (1.0 M) was added Pd/C (15 mol %) and placed under 1 atm of hydrogen. The reaction mixture was stirred as such for 24 h (until MS-analysis indicated full conversion to the desired product). The mixture was filtered over Celite and the solvent was removed under reduced pressure.

*4.5.1. Methyl 3(R)-ethyl-4(R)-methyl N-Boc L-prolinate (**16a**).* Obtained from the trisubstituted pyrroline **13a** (35 mg, 0.130 mmol) using the general procedures. The title all-*syn* 3,4-disubstituted L-proline (35 mg, quant) was obtained without further purification as a thick yellowish oil. $[\alpha]_D^{20}$ −10.1 (*c* 1.00, $CHCl_3$); IR (neat): ν_{max}=2971, 2934, 2876, 1747, 1703, 1396, 1194, 1172, 1154, 1017, 898, 767 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), mixture of rotamers: δ=4.25–4.15 (1H, 2d, *J*=9.3 Hz), 3.66–3.65 (3H, 2s), 3.50–3.45 (1H, m), 3.37–3.27 (1H, 2d, *J*=10.4 Hz), 2.33–2.30 (2H, m), 1.49–1.26 (1H, m), 1.40–1.35 (9H, 2s), 1.24–1.16 (1H, m), 1.00–0.84 (6H, m); ^{13}C NMR (100 MHz, $CDCl_3$), mixture of rotamers: δ=172.6, 172.4, 154.6, 154.0, 79.7, 62.2, 61.8, 53.9, 53.4, 51.5, 51.4, 47.2, 46.3, 34.5, 33.5, 29.4, 28.2, 19.4, 19.3, 14.1, 13.9, 12.6, 12.6; HRMS (ESIMS): calcd for $C_{14}H_{25}NO_4Na$ $[M+Na]^+$ 294.16649, found 294.16758.

*4.5.2. Methyl 3(R)-methylcyclopentyl-4(R)-methyl N-Boc L-prolinate (**16b**).* Obtained from the trisubstituted pyrroline **13b** (40 mg, 0.124 mmol) using the general procedures. The title all-*syn* 3,4-disubstituted L-proline (32 mg, 80%) was obtained without further purification as a thick yellowish oil. $[\alpha]_D^{20}$ +4.3 (*c* 1.00, $CHCl_3$); IR (neat): ν_{max}=2944, 1748, 1702, 1394, 1171, 900 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), mixture of rotamers: δ=4.26–4.18 (1H, 2d, *J*=9.5 Hz), 3.70–3.69 (3H, 2s), 3.52–3.46 (1H, m), 3.41–3.27 (1H, m), 2.59–2.45 (1H, m), 2.33–2.25 (1H, m), 1.87–1.73 (3H, m), 1.64–1.47 (4H, m), 1.44–1.38 (9H, 2s), 1.35–1.22 (2H, m), 1.10–0.99 (2H, m), 0.99 (3H, d, *J*=7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$), mixture of rotamers: δ=172.7, 172.5, 154.0, 79.7, 62.4, 62.0, 53.9, 53.4, 51.6, 51.4, 44.1, 43.2, 37.9, 34.9, 33.9, 33.1, 32.5, 32.4, 28.4, 28.3, 25.0, 14.5,

14.4; HRMS (ESIMS): calcd for $C_{18}H_{31}NO_4Na$ $[M+Na]^+$ 348.21453, found 348.21486.

*4.5.3. Methyl 3(R)-undecyl-4(R)-methyl N-Boc L-prolinate (**16c**).* Obtained from the trisubstituted pyrroline **13c** (34 mg, 0.0860 mmol) using the general procedures. Purification of the residue by flash chromatography (hexanes/EtOAc=95/5) gave the title all-*syn* 3,4-disubstituted L-proline (26 mg, 76%) as a thick yellowish oil. $[\alpha]_D^{20}$ −3.0 (*c* 1.00, $CHCl_3$); IR (neat): ν_{max}=2924, 2855, 1749, 1703, 1458, 1392, 1175, 1141, 897 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), mixture of rotamers: δ=4.29–4.19 (1H, 2d, *J*=9.4 Hz), 3.71–3.69 (3H, 2s), 3.52–3.45 (1H, m), 3.41–3.26 (1H, m), 2.50–2.37 (1H, m), 2.34–2.22 (1H, m), 1.45–1.39 (9H, 2s), 1.32–1.24 (20H, m), 0.99 (3H, d, *J*=7.2 Hz), 0.87 (3H, t, *J*=6.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$), mixture of rotamers: δ=172.6, 172.5, 154.6, 154.0, 79.7, 79.7, 62.3, 61.9, 53.9, 53.4, 51.6, 51.4, 45.4, 44.5, 31.9, 29.8, 29.6, 29.5, 29.3, 28.4, 28.3, 28.1, 26.3, 26.3, 22.7, 14.3, 14.1; HRMS (ESIMS): calcd for $C_{23}H_{43}NO_4Na$ $[M+Na]^+$ 420.30843, found 420.30919.

*4.5.4. Methyl 3(R)-[butyl-4-(1,3-dioxolanyl)]-4(R)-methyl N-Boc L-prolinate (**16d**).* Obtained from the trisubstituted pyrroline **13d** (50 mg, 0.141 mmol) using the general procedures. Purification of the residue by flash chromatography (hexanes/EtOAc=80/20) gave the title all-*syn* 3,4-disubstituted L-proline (35 mg, 70%) as a thick yellowish oil. $[\alpha]_D^{20}$ −1.3 (*c* 1.00, $CHCl_3$); IR (neat): ν_{max}=2936, 1747, 1698, 1396, 1144, 1026, 757 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), mixture of rotamers: δ=4.84 (1H, t, *J*=4.7 Hz), 4.29–4.20 (1H, 2d, *J*=9.4 Hz), 3.98–3.92 (2H, m), 3.88–3.82 (2H, m), 3.71–3.70 (3H, 2s), 3.52–3.45 (1H, m), 3.42–3.27 (1H, m), 2.51–2.39 (1H, m), 2.33–2.25 (1H, m), 1.68–1.63 (3H, m), 1.49–1.44 (2H, m), 1.45–1.39 (9H, s), 1.33–1.25 (1H, m), 0.99 (3H, d, *J*=7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$), mixture of rotamers: δ=172.5, 172.4, 154.6, 154.0, 104.2, 79.8, 79.7, 64.9, 62.2, 61.8, 53.9, 53.4, 51.6, 51.4, 45.3, 44.4, 34.7, 33.9, 33.8, 29.7, 28.4, 28.3, 26.3, 26.2, 22.5, 14.3, 14.1; HRMS (ESIMS): calcd for $C_{18}H_{31}NO_6Na$ $[M+Na]^+$ 380.20436, found 380.20434.

*4.5.5. Methyl 3(R)-phenylpropyl-4(R)-methyl N-Boc L-prolinate (**16g**).* Obtained from the trisubstituted pyrroline **13g** (16 mg, 0.0426 mmol) using the general procedures. Purification of the residue by flash chromatography (hexanes/EtOAc=80/20) gave the title all-*syn* 3,4-disubstituted L-proline (13 mg, 82%) as a thick yellowish oil. $[\alpha]_D^{20}$ −2.6 (*c* 1.00, $CHCl_3$); IR (neat): ν_{max}=2939, 1755, 1707, 1459, 1401, 1370, 1201, 1181, 1147, 898, 751, 703, 633 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), mixture of rotamers: δ=7.34–7.28 (2H, m), 7.24–7.18 (3H, m), 4.34–4.23 (1H, 2d, *J*=9.3 Hz), 3.71–3.70 (3H, 2s), 3.55–3.49 (1H, m), 3.45–3.32 (1H, m), 2.65 (2H, t, *J*=7.6 Hz), 2.55–2.45 (1H, m), 2.36–2.28 (1H, m), 1.75–1.67 (3H, m), 1.49–1.43 (9H, 2s), 1.37–1.30 (1H, m), 1.01 (3H, d, *J*=7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$), mixture of rotamers: δ=172.5, 172.4, 154.6, 154.0, 142.1, 142.1, 128.3, 125.8, 79.8, 79.7, 62.2, 61.8, 53.8, 53.3, 51.6, 51.4, 45.3, 44.4, 36.1, 36.1, 34.8, 33.9, 30.0, 28.4, 28.4, 28.4, 28.3, 28.3, 26.2, 26.1, 14.3, 14.1; HRMS (ESIMS): calcd for $C_{21}H_{31}NNaO_4$ $[M+Na]^+$ 384.21453, found 384.21572.

*4.5.6. Methyl 3(R)-benzyl-4(R)-methyl N-Boc L-prolinate (**16h**).* Obtained from the trisubstituted pyrroline **13h** (18.5 mg, 0.0533 mmol) using the general procedures. Purification of the residue by flash chromatography (hexanes/EtOAc=80/20) gave the title all-*syn* 3,4-disubstituted L-proline (13 mg, 70%) as a thick yellowish oil. $[\alpha]_D^{20}$ −2.1 (*c* 0.80, $CHCl_3$); IR (neat): ν_{max}=2982, 2941, 1754, 1702, 1459, 1440, 1398, 1370, 1256, 1201, 1178, 1147, 1118, 1023, 991, 913, 773, 736, 703, 633 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), mixture of rotamers: δ=7.25–7.18 (2H, m), 7.17–7.10 (3H, m), 4.33–4.23 (1H, 2d, *J*=9.0 Hz), 3.61–3.59 (3H, 2s), 3.47–3.39 (1H, m), 3.33–3.18 (1H, m), 2.92–2.76 (2H, m), 2.51–2.44 (1H, m), 2.19–2.12 (1H, m), 1.39–1.33 (9H, 2s), 1.00 (3H, d, *J*=7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$), mixture of rotamers: δ=172.3, 154.0, 139.6, 139.5, 128.5, 128.4, 126.2, 79.9, 62.2, 61.8, 53.7, 53.2, 51.7, 51.5, 46.1, 45.2, 34.5, 33.7, 31.8, 31.7, 29.7, 28.4, 28.3, 14.5, 14.3; HRMS (ESIMS): calcd for $C_{19}H_{28}NO_4$ $[M+H]^+$ 334.20128, found 334.20289.

*4.5.7. Methyl 3(R)-(ρ-methoxybenzyl)-4(R)-methyl N-Boc L-prolinate (**16i**).* Obtained from the trisubstituted pyrroline **13i** (30 mg, 0.0795 mmol) using the general procedures. Purification of the residue by flash chromatography (hexanes/EtOAc=80/20) gave the title all-*syn* 3,4-disubstituted L-proline (20 mg, 67%) as a thick yellowish oil. $[\alpha]_D^{20}$ −4.8 (*c* 0.50, $CHCl_3$); IR (neat): ν_{max}=2927, 1747, 1697, 1512, 1392, 1246, 1173, 1145, 1113, 1033, 901, 818 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), mixture of rotamers: δ=7.15–7.10 (2H, m), 6.86–6.81 (2H, m), 4.38–4.28 (1H, 2d, *J*=9.0 Hz), 3.78 (3H, s), 3.68–3.66 (3H, 2s), 3.52–3.40 (1H, m), 3.40–3.27 (1H, m), 2.92–2.76 (2H, m), 2.52–2.46 (1H, m), 2.25–2.17 (1H, m), 1.45–1.40 (9H, 2s), 1.05 (3H, d, *J*=7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$), mixture of rotamers: δ=172.4, 172.1, 158.0, 154.6, 154.0, 131.6, 131.5, 129.4, 113.9, 113.8, 79.9, 62.1, 61.8, 55.2, 53.8, 53.2, 51.7, 51.5, 46.4, 45.5, 34.4, 33.7, 30.9, 30.8, 28.4, 28.3, 14.4, 14.3; HRMS (ESIMS): calcd for $C_{20}H_{29}NO_5Na$ $[M+Na]^+$ 386.19379, found 386.19334.

*4.5.8. Methyl 3(R)-(ρ-fluorobenzyl)-4(R)-methyl N-Boc L-prolinate (**16j**).* Directly obtained from the allylic alcohol **11j** (39 mg, 0.107 mmol) using method A. Purification of the residue by flash chromatography (hexanes/EtOAc=80/20) gave the title all-*syn* 3,4-disubstituted L-proline (12 mg, 32%) as a thick yellowish oil. $[\alpha]_D^{20}$ +0.8 (*c* 1.00, $CHCl_3$); IR (neat): ν_{max}=2932, 1756, 1706, 1514, 1400, 1178, 1148, 908 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), mixture of rotamers: δ=7.19–7.14 (2H, m), 7.01–6.95 (2H, m), 4.39–4.28 (1H, 2d, *J*=9.0 Hz), 3.67–3.65 (3H, 2s), 3.54–3.48 (1H, m), 3.41–3.27 (1H, m), 2.92–2.76 (2H, m), 2.57–2.50 (1H, m), 2.25–2.19 (1H, m), 1.46–1.40 (9H, 2s), 1.05 (3H, d, *J*=7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$), mixture of rotamers: δ=172.2, 172.0, 162.6, 160.1, 154.6, 153.9, 135.2, 135.1, 135.1, 129.9, 129.8, 115.3, 115.3, 115.1, 115.1, 80.0, 79.9, 62.0, 61.7, 53.7, 53.2, 51.7, 51.5, 46.3, 45.4, 34.5, 33.7, 31.0, 30.9, 29.7, 28.4, 28.3, 14.4, 14.3; HRMS (ESIMS): calcd for $C_{19}H_{26}NFO_4Na$ $[M+Na]^+$ 374.17556, found 374.17381.

4.6. (2*S*)-1-*tert*-Butyl-2-methyl-3-ethyl-4-methyl-*d*3-2,5-dihydro-1*H*-pyrrole-1,2-dicarboxylate (19)

Under argon and in a flame-dried flask, the starting enone **10a** (124 mg, 0.461 mmol) was dissolved in dry THF (2.5 mL) and commercial solution of $LaCl_3{\cdot}2LiCl$ (0.6 in THF, 0.810 mL, 0.484 mmol) was added at rt. The mixture was allowed to stir as such for 1 h, then it was cooled to −78 °C and CD_3MgI freshly prepared from CD_3I (4.6 mmol) and Mg turnings (6.9 mmol) in Et_2O (3 mL)was added dropwise. The resulting brownish solution was stirred at −78 °C for 1 h, then quenched at −78 °C with aqueous saturated NH_4Cl. The biphasic mixture was separated and the aqueous phase was extracted three times with Et_2O (3×10 mL). The combined organic layers were washed with brine and dried over Na_2SO_4, and the solvent was removed under reduced pressure. Purification of the residue by flash chromatography gave the title compound as yellowish oil (81 mg, 61%). R_f=0.4 (hexanes/EtOAc=60/40), [$KMnO_4$]. ^1H NMR (400 MHz, $CDCl_3$), mixture of rotamers: δ=5.82–5.77 (1H, q, *J*=7.2 Hz), 4.91–4.83 (1H, 2s), 4.09–3.86 (1H, 2s), 3.82–3.71 (1H, 2s), 3.79–3.77 (3H, 2s), 3.27–3.25 (1H, 2s), 1.76–1.74 (3H, 2s), 1.44–1.41 (9H, 2s); HRMS

(ESIMS): calcd for $C_{14}H_{20}NO_5Na$ $[M+Na]^+$ 311.16567, found 311.16594.

4.7. (2*S*)-1-*tert*-Butyl-2-methyl-3-ethyl-4-methyl-*d*3-2,5-dihydro-1*H*-pyrrole-1,2-dicarboxylate (20)

The starting allylic alcohol **19** (50 mg, 0.174 mmol) was dissolved in 1 mL EtOAc and $Pd(OH)_2$ (10 mol %) was added. The resulting mixture was purged with hydrogen and stirred for 16 h under hydrogen atmosphere. The mixture was filtered over Celite and the solvent was removed under reduced pressure. Purification of the residue by flash chromatography gave the title compound as yellowish oil (32 mg, 68%). R_f=0.5 (hexanes/EtOAc=80/20), [$KMnO_4$]. ^{1}H NMR (400 MHz, $CDCl_3$), mixture of rotamers: δ=4.95–4.86 (1H, 2s), 4.19–4.17 (1H, m), 4.07–4.04 (1H, m), 3.76–3.73 (3H, 2s), 2.23–2.20 (1H, m), 1.96–1.94 (1H, m), 1.49–1.44 (9H, 2s), 1.04–1.00 (3H, t, J=7.6 Hz); HRMS (ESIMS): calcd for $C_{14}H_{20}NO_4Na$ $[M+Na]^+$ 295.17076, found 295.16976.

4.8. (2*S*,4*S*,*E*)-1-*tert*-Butyl 2-methyl 4-acetoxy-3-ethylidene-4-methylpyrrolidine-1,2-dicarboxylate (21)

A solution of the allylic alcohol **11a** (148 mg, 0.500 mmol) in CH_2Cl_2 (2.5 mL) was cooled to 0 °C and DMAP (cat.), NEt_3 (88 μL, 0.600 mmol), and Ac_2O (60 μL, 0.600 mmol) were added. The reaction mixture was allowed to warm up to rt and stirred for 20 min, after which full conversion was observed. The reaction mixture was thus quenched with a 1 N HCl solution (5 mL), the aqueous and organic phases were separated and the aqueous phase was further extracted with EtOAc (3×5 mL). The residue was purified by flash chromatography (hexanes/EtOAc=80/20) to give the allylic acetate **21** (170 mg, 99%) as a colorless liquid. R_f=0.5 (hexanes/EtOAc=70/30), [$KMnO_4$]. $[\alpha]_D^{20}$ +38.4 (*c* 1.00, $CHCl_3$); IR (neat): ν_{max}=2964, 2936, 1741, 1702, 1400, 1365, 1244, 1202, 1170, 1109, 1014, 900, 769 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), mixture of rotamers: δ=5.95–5.79 (1H, m), 4.99–4.87 (1H, 2s), 4.02–3.95 (1H, 2d, J=12 Hz), 3.67 (3H, s), 3.47–3.40 (1H, 2d, J=12 Hz), 1.90–1.88 (3H, d, J=7.2 Hz), 1.83–1.81 (3H, 2d, J=6.8 Hz), 1.62 (3H, s), 1.42–1.39 (9H, 2s); ^{13}C NMR (100 MHz, $CDCl_3$), mixture of rotamers: δ=170.9, 170.8, 170.7, 170.5, 154.7, 153.9, 137.1, 136.9, 126.9, 126.3, 84.5, 83.5, 80.8, 80.7, 60.8, 60.2, 57.7, 57.6, 52.5, 52.3, 28.7, 28.6, 28.6, 22.4, 22.3, 21.8, 21.5, 15.3, 15.2; HRMS (ESIMS): calcd for $C_{14}H_{25}NO_6Na$ $[M+Na]^+$ 350.15621, found 350.15741.

4.9. (2*S*,4*S*,*E*)-1-*tert*-Butyl 2-methyl 4-(*tert*-butyl)-3-ethylidene-4-hydroxypyrrolidine-1,2-dicarboxylate (28)

Under argon and in a flame-dried flask, the enone **10a** (195 mg, 0.700 mmol) was dissolved in dry THF (3.5 mL) and a commercial solution of $LaCl_3 \cdot 2LiCl$ (0.6 M in THF, 1.17 mL, 0.700 mmol) was added at rt. The mixture was allowed to stir as such for 1 h, then it was cooled to −78 °C and added MeMgBr (350 μL, 3.0 M in Et_2O, 1.05 mmol) dropwise. The resulting brownish solution was stirred at −78 °C for 1 h, then quenched at −78 °C with aqueous saturated NH_4Cl (10 mL). The biphasic mixture was separated and the aqueous phase was extracted with Et_2O (3×10 mL). Special care was taken to avoid acidic wash (no 1 M HCl), as analogous intermediates were shown to decompose rapidly under such conditions. The solvent was removed under reduced pressure without heating. Purification of the residue by flash chromatography gave the title compound as yellowish oil (118 mg, 48%). R_f=0.4 (hexanes/EtOAc=70/30), [$KMnO_4$]. $[\alpha]_D^{20}$ −4.7 (*c* 1.00, $CHCl_3$); IR (neat): ν_{max}=3463, 2963, 1750, 1700, 1393, 1371, 1165, 1125, 1096, 1017, 908, 858, 771 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), mixture of rotamers: δ=5.91–5.89 (1H, m), 4.90–4.81 (1H, 2s), 3.97–3.94 (1H, 2s), 3.88–3.83 (1H, 2d, J=11.6 Hz), 3.78–3.76 (3H, 2s), 3.46–3.41 (1H, 2d, J=11.2 Hz), 1.76–1.75 (3H, d, J=4.0 Hz), 1.47–1.44 (9H, 2s), 0.99–0.98 (9H, 2s); ^{13}C NMR (100 MHz, $CDCl_3$), mixture of rotamers: δ=173.1, 139.8, 139.3, 125.2, 83.4, 82.7, 81.0, 80.9, 65.1, 62.5, 62.0, 57.4, 56.6, 56.0, 52.9, 52.6, 37.5, 28.7, 28.6, 14.9, 14.8; HRMS (ESIMS): calcd for $C_{14}H_{29}NO_6Na$ $[M+Na]^+$ 350.19275, found 350.19379.

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Supplementary data

These data include ^{1}H NMR and ^{13}C NMR spectra of compounds **10a–j**, **11a–j**, **12**, **13a–g**, **14**, **15**, **16a–e**,**g–j** and **21**. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2013.11.040.

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