RSC Advances

PAPER

View Article Online
View Journal | View Issue

Cite this: *RSC Adv.*, 2014, **4**, 22387

Received 11th March 2014
Accepted 28th April 2014

DOI: 10.1039/c4ra02124j

www.rsc.org/advances

First example of a Prins–Ritter reaction on terpenoids: a diastereoselective route to novel 4-amido-octahydro-2*H*-chromenes†

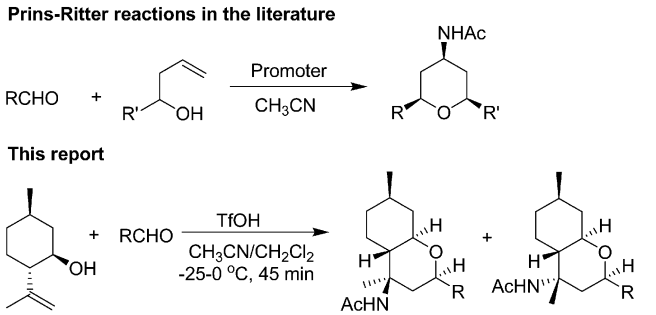
Barnali Sarmah,[a] Gakul Baishya*[a] and Rajani K. Baruah[b]

(−)-Isopulegol was subjected to a triflic acid-promoted three-component Prins–Ritter reaction with a series of aldehydes to produce a library of novel 4-acetamido-octahydro-2*H*-chromene derivatives in good yields and high diastereoselectivities.

Introduction

The highly functionalized tetrahydropyran ring, the key structural motif of many biologically and synthetically important natural products, has attracted a great deal of attention in the field of synthetic organic chemistry.[1] The construction of tetrahydropyran rings is generally achieved in a single step chemical process *via* the well-known Prins cyclization reaction of homoallylic alcohols with aldehydes or ketones.[2] Recently, one-pot, three-component reactions have shown their potential in various applications of pharmaceutical chemistry such as the production of structural scaffolds and in combinatorial libraries for drug discovery.[3] The Prins cyclization method could be utilized as an initiator of a tandem three-component reaction because the carbocation formed during the course of the reaction has to be quenched with various nucleophiles.[4] Moreover, the technique of a tandem reaction is also a valuable synthetic tool that plays an important role in the synthesis of natural product-like molecules.[5] The major advantage of a tandem reaction is the consecutive formation of several covalent bonds, including C–C, C–O, and C–N, among others, by a single catalyst in one-pot. Again, amino tetrahydropyrans are the core structures of many natural products such as ambrucitin VS, oligomer of glycamino acids, sialic acid and dysiherbaine, *etc.*[7] Various applications[8] of these compounds in photographic plates as well as in host–guest chemistry are well documented in the literature. The sequence of the Prins–Ritter reaction could be utilized as the best synthetic method to build the six membered ring of 4-amino tetrahydropyran derivative efficiently in a single step reaction (Scheme 1).[6] It is also well established that the Prins–Ritter reaction sequence can be efficiently utilized for the synthesis of optically pure natural alkaloids (−)-halosaline and (−)-norallosedamine without loss of their optical purities.[6]

Perron and Albizati first developed a tandem Prins–Ritter sequence wherein 4-acetamido-pyranosides were synthesized through a $SnCl_4$ mediated reaction of orthoesters with homoallylic alcohols in acetonitrile.[4e] Willis and co-workers also reported the Prins–Ritter tandem cyclization of acetal of a homoallylic alcohol in the presence of triflic acid in acetonitrile.[9] Recently, Yadav *et al.* also demonstrated the tandem Prins–Ritter reaction of homoallylic alcohols, aldehydes or ketones and nitriles in two different reports using a catalytic mixture $CeCl_3$–acetyl chloride[10a] and phosphomolybdic acid.[10b] The Sakurai–Prins–Ritter reaction sequence was also efficiently employed to synthesize synthetically important 4-acylamino-2,6-disubstituted tetrahydropyran derivatives.[11] Again, 2*H*-chromene[12] is also found to be the core structural motif of several biologically active natural products such as calonolide F, which was isolated from *Calophyllum teysmannii*.[13] Calonolide F mainly exhibits anti-HIV activity, whereas its synthetic analogues show anti-hypertensive[14] and anti-ischaemic[15] activities. Although there are many existing reports on Prins–Ritter[16] and Sakurai–Prins–Ritter reactions in the literature, to the best of our knowledge, this is the first example of the synthesis of



Scheme 1 Prins–Ritter reaction sequence.

[a]*Natural Products Chemistry Division, CSIR-North East Institute of Science & Technology, Jorhat-785006, India. E-mail: b.gakul@gmail.com; Fax: +91-376-2370011*

[b]*Analytical Chemistry Division, CSIR-North East Institute of Science & Technology, Jorhat-785006, India. Fax: +91-376-2370011*

† CCDC 968993. For crystallographic data in CIF or other electronic format see DOI: 10.1039/c4ra02124j

novel 4-acetamido-octahydro-2*H*-chromene derivatives *via* the Prins–Ritter reaction of (−)-isopulegol with aldehydes.

As a part of our ongoing research programme on the Prins cyclization reaction,[17] we report herein the successful execution of the Prins–Ritter strategy for the synthesis of a library of novel 4-acetamido-octahydro-2*H*-chromene derivatives from (−)-isopulegol and aldehydes using triflic acid as a promoter under very mild conditions (Scheme 1, This report).

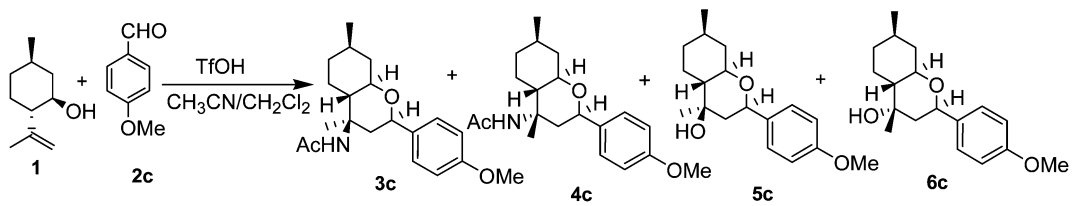
Results and discussions

In search of optimal reaction conditions, we first attempted the reaction of (−)-isopulegol (1 mmol) with *p*-anisaldehyde (1.2 mmol) using 1 equivalent of triflic acid (1 mmol) as a promoter in acetonitrile at 24 °C. But the reaction gave a complex mixture of products. Repeating the reaction at 0 °C as well as −10 °C failed to control the formation of by-products. As such, we considered performing the reaction at a lower temperature to address the problem of formation of multiple products. Thus, we performed the same reaction at −20 °C using one equivalent of triflic acid. This time, the reaction proceeded smoothly affording a diastereomeric mixture of Prins–Ritter products **3c** and **4c**, as confirmed by their ^{1}H NMR spectra, along with the diastereomeric mixture of the normal Prins cyclized products, **5c** and **6c**. However, the yield of the reaction was very poor (37%). To obtain a better yield, we also increased the amount of TfOH to 1.5, 2.0 and 3.0 equivalents to obtain the diastereomeric mixture of Prins–Ritter products in 53%, 72% and 70% yields, respectively. However, 10–13% yield of the normal Prins cyclized product (**5c** and **6c**) was also isolated in each case. In subsequent experiments, we also tried to stop the formation of the normal Prins cyclized product by decreasing the temperature to −25 °C, −40 °C and −50 °C using 2.0 equivalent of triflic acid. We found that the formation of the normal Prins cyclized product could not be completely avoided and 8–9% yield of **5c** and **6c** were also obtained in each case. Thus, the optimal reaction conditions involved the use of (−)-isopulegol **1** (1 mmol) with *p*-anisaldehyde **2c** (1.2 mmol) and a solution of 2 equivalents of triflic acid (2 mmol) as the promoter in 1 mL CH_2Cl_2 in acetonitrile (1 mL) at −25 °C (Table 1).

After optimization of the reaction conditions, we explored the general applicability and scope of this protocol with various aromatic and aliphatic aldehydes; the results are presented in the Table 2.

The exploration of this Prins–Ritter protocol began with the reaction of (−)-isopulegol with various aromatic and hetero-aromatic aldehydes. Various substituted aromatic aldehydes including *p*-tolualdehyde, *p*-isopropylbenzaldehyde, *m*-nitrobenzaldehyde, *p*-chlorobenzaldehyde, 3,4-dichlorobenzaldehyde and *p*-bromobenzaldehyde underwent the Prins–Ritter reaction smoothly to produce their corresponding 4-acetamido-octahydro-2*H*-chromene derivatives under the optimized reaction conditions (entries d–i, Table 2). The crude products were purified by column chromatography to afford pure 4-acetamido-octahydro-2*H*-chromenes. However, the ^{1}H NMR spectra of the pure products after column chromatography revealed the presence of a mixture of two diastereomers. In order to separate the two diastereomers, we performed a re-crystallization and successfully separated both species as optically pure diastereomers. Both aromatic aldehydes bearing electron donating and electron withdrawing substituents afforded 4-acetamido-octahydro-2*H*-chromene derivatives in good yields; however, the ratios of diastereomers obtained after re-crystallization were higher in the case of aromatic aldehydes with electron donating substituents. Unsubstituted aromatic

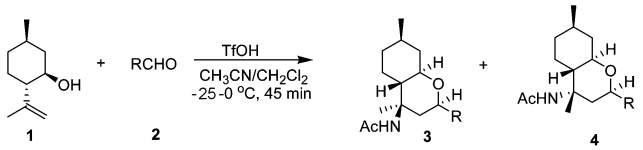
Table 1 Reaction condition optimization studies using (−)-isopulegol 1 and *p*-anisaldehyde 2c[a]



Entry	TfOH (equiv.)	Temperature	Time	Yield[b] (%) **3c** + **4c**	Yield[b] (%) **5c** + **6c**
1	1.0	24 °C	1 h	—	—
2	1.0	0 °C	1 h	—	—
3	1.0	−10 °C	1 h	—	—
4	1.0	−20 °C	45 min	37	12
5	1.5	−20 °C	45 min	53	13
6	2.0	−20 °C	45 min	72	10
7	3.0	−20 °C	45 min	70	14
8	2.0	−25 °C	45 min	76	7
9	2.0	−40 °C	45 min	76	8
10	2.0	−50 °C	45 min	74	7

[a] Reaction conditions: reaction performed with 1.2 mmol of **2c** and 1 mmol of **1** at a1 : 1 ratio of CH_3CN/CH_2Cl_2 in 2 mL solution. [b] Yields are for isolated products as mixtures.

Table 2 Scope of the triflic acid promoted Prins–Ritter reaction of (−)-isopulegol



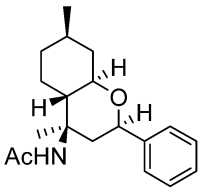
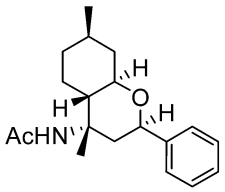
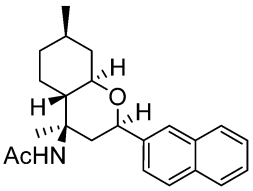
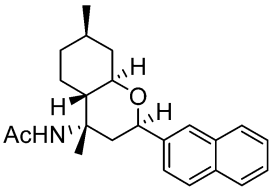
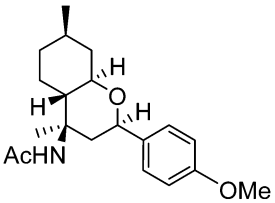
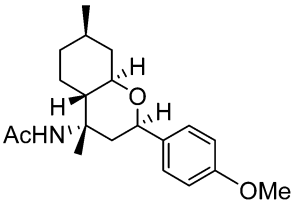
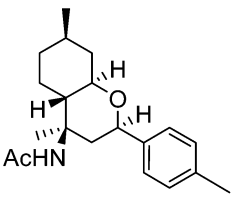
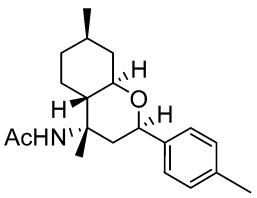
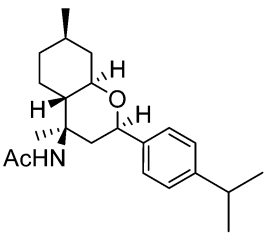
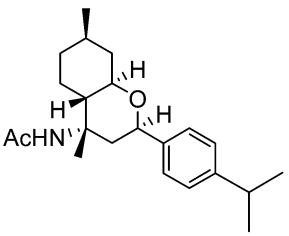
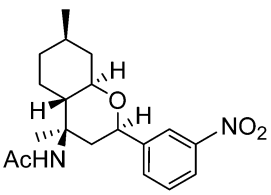
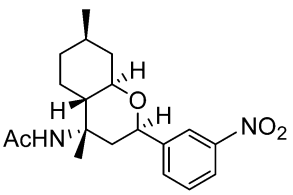
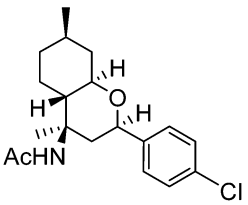
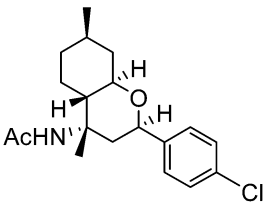
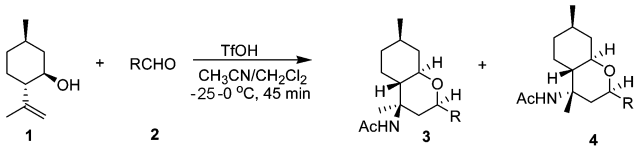
Entry	Aldehyde R=	Product **3**[a]	Product **4**[a]	% Yield[b]	Ratio **3** : **4**[c]
a	Ph			62	5 : 1
b	2-Naphthyl			68	4 : 1
c	4-MeO-Ph			76	5 : 1
d	4-Me-Ph			72	5 : 1
e	4-iso-Propyl-Ph			76	4 : 1
f	3-NO_2-Ph			64	3.5 : 1[d]
g	4-Cl-Ph			70	5 : 1

Table 2 (*Contd.*)



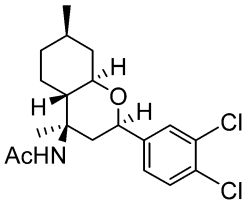
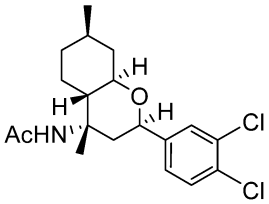
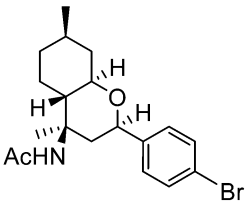
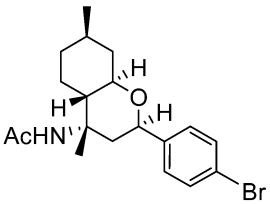
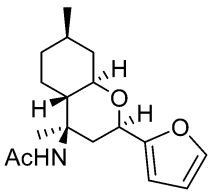
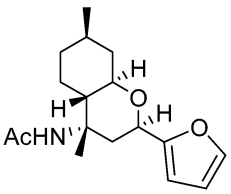
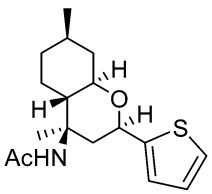
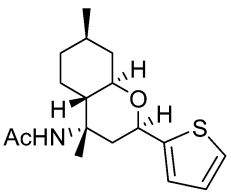
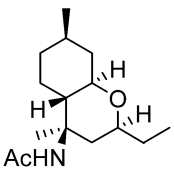
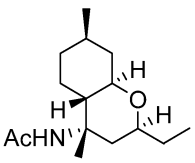
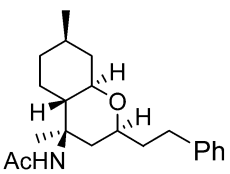
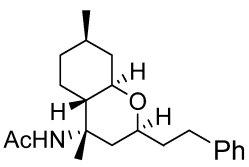
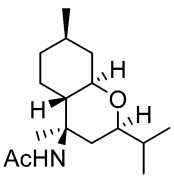
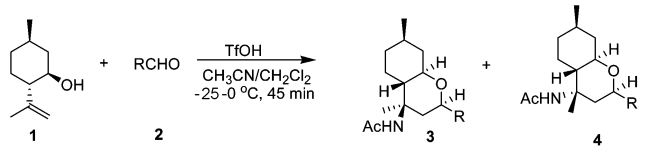
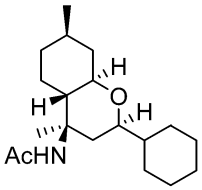
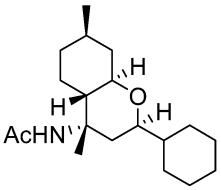
Entry	Aldehyde R=	Product **3**[a]	Product **4**[a]	% Yield[b]	Ratio **3** : **4**[c]
h	3,4-Cl_2-Ph			60	5 : 1
i	4-Br-Ph			62	4 : 1
j	2-Furfuryl			67	3 : 1
k	2-Thiophenyl			64	3.5 : 1
l	*n*-Ethyl			60	2 : 1
m	3-Phenyethyl			62	2 : 1
n	iso-Propyl			58	—[e]

Table 2 (*Contd.*)



Entry	Aldehyde R=	Product **3**[a]	Product **4**[a]	% Yield[b]	Ratio **3 : 4**[c]
o	Cyclohexyl			65	3 : 1

[a] Products **3** and **4** were characterized by their ^{1}H NMR, ^{13}C NMR, mass and IR spectra. [b] Combined isolated yields. [c] Diastereomeric ratios were obtained from their isolated yields. [d] Diasteromeric ratio was obtained from its ^{1}HNMR spectrum. [e] Major isomer **3n** was exclusively obtained and **4n** was not isolated in a trace amount.

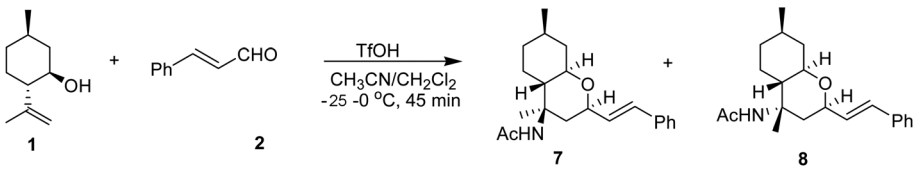
aldehydes such as benzaldehyde and 2-napthaldehyde also underwent a Prins–Ritter reaction to afford their corresponding 4-acetamido-octahydro-4*H*-chromene in good yields and good diastereoselectivities (entries a & b, Table 2). Interestingly, the Prins–Ritter reaction of heteroaromatic aldehydes including 2-furfuraldehye and 2-thiophene carbaldehyde with (−)-isopulegol under the same reaction condition also afforded their corresponding acetamido chromene derivatives in good yields and good diastereoselectivities (entries j & k, Table 2).

To confirm the utility of this protocol, various aliphatic aldehydes were also reacted with (−)-isopulegol and acetonitrile under the same reaction conditions. For example, propanal, 3-phenyl propanal, cyclohexyl carbaldehyde and isobutaraldehyde also underwent a smooth Prins–Ritter reaction with (−)-isopulegol and acetonitrile in the presence of 2 equivalents of triflic acid at −25 °C to yield their corresponding 4-acetamido-octahydro-2*H*-chromenes (entries l–o, Table 2). Surprisingly, the products were also obtained in good yields and good diastereoselectivities using these aldehydes. However, in the case of aliphatic aldehydes, the diastereomers produced in each reaction were separated by simple silica gel column chromatography.

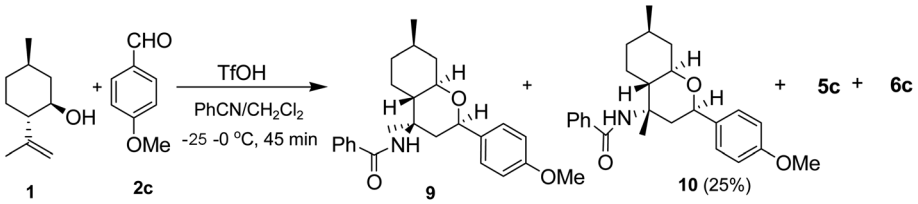
Furthermore, it has been established that this methodology can be extended to conjugated aldehydes and works well with cinnamaldehyde to furnish the corresponding 4-acetamido-octahydro-2*H*-chromenes **7** and **8** in moderate yield and good diastereoselectivity (**7 : 8** = 4 : 1) (Scheme 2). Like other aliphatic aldehydes, the diastereomers obtained in this case were also separated by silica gel column chromatography.

In subsequent experiments, we also explored the addition of diversity at the 4-position of the chromene derivatives using different nitrile molecules. Thus, different nitrile molecules including benzonitrile, acrylonitrile, piperonitrile were reacted with (−)-isopulegol and *p*-anisaldehyde in three different reactions. We found that only benzonitrile underwent the Prins–Ritter sequence to afford the corresponding 4-benzamido-octahydro-2*H*-chromene derivatives **9** and **10** in good yield. In addition, the diastereoselectivity could not be achieved from the isolated yield because isomer **9** could not be isolated in its pure form by normal silica gel column chromatography (Scheme 3).

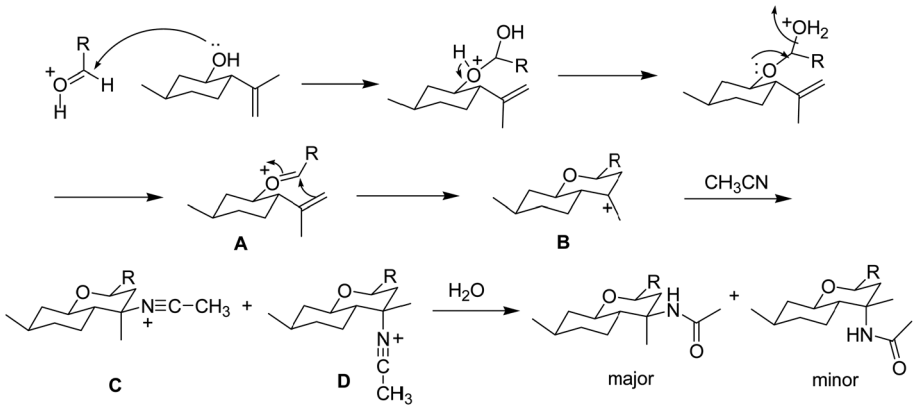
A possible mechanism for this important transformation has been proposed in Scheme 4. It has been shown that the aldehyde group is first protonated by the triflic acid that has been attacked by the hydroxyl group of the isopulegol molecule. The subsequent proton transfer followed by the removal of a water molecule leads to the oxocarbenium ion A that undergoes a Prins cyclization *via* its common *cis*-selective pathway to produce the tetrahydropyranyl tertiary carbocation B. The nucleophile (acetonitrile) present in the reaction medium attacks the carbocation B from either sides to give the intermediates C and D, which under hydrolysis give the desired products. The major isomer possesses the equatorial acetamide



Scheme 2



Scheme 3 Synthesis of 4-benzamido-octahydro-2*H*-chromen from (−)-isopulegol.



Scheme 4 Mechanism of the Prins–Ritter reaction of (−)-isopulegol.

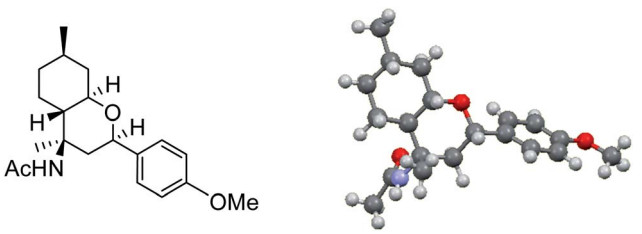


Fig. 1 Single X-ray crystallographic structure of the compound **3c**.

group, which was confirmed by the single-X-ray crystallography of **3c** (Fig. 1) and NOESY experiment of **4c**. These results indicate that the trapping of the carbocation B favors the equatorial side.

Conclusion

In conclusion, an operationally simple method has been developed for the diastereoselective synthesis of novel 4-acetamido-octahydro-2*H*-chromene derivatives using a one-pot sequential Prins–Ritter reaction of (−)-isopulegol with aldehydes in the presence of triflic acid as the promoter under very mild reaction conditions. A wide range of non-substituted and substituted aromatic aldehydes with both electron donating and electron withdrawing substituents underwent a Prins–Ritter reaction with (−)-isopulegol. This protocol was also equally effective with various aliphatic and conjugated aldehydes. The triflic acid promoted Prins–Ritter reaction offers a new synthetic route for the synthesis of novel 4-amido-octahydro-2*H*-chromene derivatives in a single step.

Experimental

General methods

Melting points were measured using a Buchi B-540 melting point apparatus and are uncorrected. IR spectra were recorded on a SHIMADZU FTIR-8400. NMR spectra were recorded on a Bruker DPX 300 MHz, AV500 Advance-III 500 MHz and Jeol JNM 400 MHz spectrometers using tetramethylsilane (TMS) as an internal standard. Mass spectra were recorded on an ESQUIRE 3000 Mass spectrometer. All the commercially available reagents were used without further purification. All experiments were monitored by thin layer chromatography using aluminum pre-coated silica gel TLC plates (Merck). After elution, the spots were visualized under UV illumination at 254 nm. Further visualization was achieved by staining the anisaldehyde charring solution. Column chromatography was performed on silica gel (100–200 mesh, Rankem) using an appropriate ethyl acetate–hexane mixture. Specific rotation values were measured on a PerkinElmer Polarimeter model 343.

General procedure for the preparation of compounds 3 and 4. To a solution of (−)-isopulegol (1.0 mmol), aldehyde **1** (1.2 mmol) and dry acetonitrile (1 mL), a solution of triflic acid (2.0 mmol in 1 mL CH_2Cl_2) was added dropwise and the mixture was stirred at −25 °C for 30 min. The reaction mixture was allowed to warm up to 0 °C over 45 min. After the completion of the reaction as determined by TLC, 10 mL of a saturated aq. $NaHCO_3$ solution was added to the reaction mixture and extracted with ethyl acetate (3 × 10 mL). The organic layer was washed with brine (1 × 10 mL) and dried over anhydrous sodium sulphate. The organic layer was concentrated under

rotary evaporator and separated using column chromatography on silica gel (100–200 mesh) using 3 : 7 ethyl acetate–hexane as the eluent to obtain the Prins–Ritter products **3** and **4** (as diastereomeric mixture as confirmed by its ^{1}H NMR spectrum). The two diastereomers were separated from the mixture by re-crystallization from hexane. The structure of compounds **5c** and **6c** was confirmed by comparing their analytical data with those reported in the literature.[17a]

***N*-(4,7-Dimethyl-2-phenyl-octahydro-chromen-4-yl)-acetamide (3a).** White solid; m.p. 197.4 °C. $[\alpha]_D^{20} = +6.0$ (*c* 0.1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36–7.20 (m, 5H), 5.30 (s, 1H), 4.53 (dd, $J = 11.7$, 1.8 Hz, 1H), 3.47 (td, $J = 10.4$, 4.2 Hz, 1H) 2.41 (dd, $J = 13.2$, 2.1 Hz, 1H), 2.21–2.04 (m, 3H), 1.91 (s, 3H), 1.76–1.71 (m, 2H), 1.47 (s, 3H), 1.19–0.99 (m, 4H), 0.95 (d, $J = 6.48$ Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.4, 142.3, 128.2, 127.3, 126.0, 75.9, 75.7, 55.1, 47.7, 45.6, 41.5, 34.3, 31.3, 24.7, 23.5, 22.1, 18.9. IR ($CHCl_3$): 3306.2, 2925.0, 2857.5, 1650.1, 1551.3 cm^{-1}. ESI (MS): $m/z = 324$ $[M + Na]^+$. Anal. calcd for $C_{19}H_{27}NO_2$: C, 75.71; H, 9.03; N, 4.65; found: C 75.67, H 9.07, N 4.60.

***N*-(4,7-Dimethyl-2-phenyl-octahydro-chromen-4-yl)-acetamide (4a).** Gummy liquid. $[\alpha]_D^{20} = +30.0$ (*c* 0.3). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35–7.19 (m, 5H), 5.30 (s, 1H), 4.57 (dd, $J = 11.6$, 1.6 Hz, 1H), 3.45 (td, $J = 10.4$, 4.3 Hz, 1H), 3.13 (dd, $J = 13.9$, 1.8 Hz, 1H), 2.03 (s, 3H), 1.97–1.91 (m, 3H), 1.47–1.43 (m, 2H), 1.42 (s, 3H), 1.00–0.97 (m, 4H), 0.95 (d, $J = 6.3$ Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.7, 142.2, 128.2, 127.2, 125.8, 74.8, 53.9, 50.7, 42.7, 41.5, 34.3, 31.3, 24.8, 24.5, 22.9, 22.1. IR ($CHCl_3$): 3336.8, 2925.9, 2869.2, 1655.3, 1535.5 cm^{-1}. ESI (MS): $m/z = 324$ $[M + Na]^+$.

***N*-(4,7-Dimethyl-2-naphthalen-2-yl-octahydro-chromen-4-yl)-acetamide (3b).** White solid; m.p. 214.5 °C. $[\alpha]_D^{20} = +7.0$ (*c* 0.1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.82–7.77 (m, 4H), 7.50–7.39 (m, 3H), 5.35 (s, 1H), 4.70 (dd, $J = 11.7$, 1.7 Hz, 1H), 3.53 (dt, $J = 14.4$, 4.1 Hz, 1H), 2.48 (dd, $J = 13.2$, 2.1 Hz, 1H), 2.31–2.27 (m, 1H), 2.08–2.04 (m, 1H), 1.91 (s, 3H), 1.83–170 (m, 3H), 1.51 (s, 3H), 1.24–0.97 (m, 4H), 0.95 (d, $J = 6.5$ Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.5, 139.7, 133.3, 132.9, 127.9, 127.5, 125.8, 125.5, 124.6, 124.4, 76.0, 75.8, 55.2, 47.7, 45.5, 41.6, 34.4, 31.4, 24.7, 23.6, 22.1, 18.9. IR ($CHCl_3$): 3312.4, 2925.7, 2858.4, 1658.8, 1548.3 cm^{-1}. ESI (MS): $m/z = 374$ $[M + Na]^+$. Anal. calcd for $C_{23}H_{29}NO_2$: C 78.59, H 8.32, N 3.99; found: C 78.55, H 8.36, N 3.97.

***N*-(4,7-Dimethyl-2-naphthalen-2-yl-octahydro-chromen-4-yl)-acetamide (4b).** Semisolid. $[\alpha]_D^{20} = +25.0$ (*c* 0.2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.82–7.77 (m, 4H), 7.50–7.39 (m, 3H), 5.35 (s, 1H), 4.73 (d, $J = 10.6$ Hz, 1H), 3.52 (td, $J = 13.9$, 1.6 Hz, 1H), 3.20 (dd, $J = 13.8$, 1.8 Hz, 1H), 2.07 (s, 3H), 2.05–1.48 (m, 4H), 1.38–1.19 (m, 4H), 1.25 (s, 3H), 0.88 (d, $J = 7.1$ Hz, 3H), 0.87–0.85 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.8, 139.9, 133.3, 132.8, 127.9, 127.8, 127.5, 125.8, 125.5, 124.3, 124.2, 77.2, 74.9, 53.9, 50.7, 42.8, 41.5, 34.4, 31.3, 29.7, 24.5, 22.9, 22.1. IR ($CHCl_3$): 3337.9, 2926.7, 2868.8, 1656.0, 1532.7 cm^{-1}. ESI (MS): $m/z = 374$ $[M + Na]^+$.

***N*-[2-(4-Methoxy-phenyl)-4,7-dimethyl-octahydro-chromen-4-yl]-acetamide (3c).** White solid; m.p. 199.6 °C. $[\alpha]_D^{20} = -2.0$ (*c* 0.16). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.29 (d, $J = 7.6$ Hz, 2H), 6.86 (m, $J = 7.6$ Hz, 2H), 5.26 (s, 1H), 4.48 (dd, $J = 11.6$, 1.9 Hz, 1H) 3.77 (s, 3H), 3.46 (td, 1H, $J = 10.4$, 4.2 Hz), 2.36 (dd, $J = 13.2$, 2.2 Hz, 1H), 2.23–1.98 (m, 2H), 1.92 (s, 3H), 1.75–1.71 (m, 3H), 1.46 (s, 3H), 1.17–0.98 (m, 4H), 0.94 (d, $J = 6.4$ hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.5, 158.9, 134.5, 127.4, 113.6, 75.9, 75.3, 55.2, 55.1, 47.5, 45.4, 41.6, 34.3, 31.3, 24.6, 23.5, 22.1, 18.9. IR ($CHCl_3$): 3310.4, 2948.9, 2926.4, 2858.7, 1654.2, 1514.6 cm^{-1}. ESI (MS): $m/z = 354$ $[M + Na]^+$, Anal. calcd for $C_{20}H_{29}NO_3$: C 72.47, H 8.82, N 4.23; found: C 72.42, H 8.76, N 4.19.

***N*-[2-(4-Methoxy-phenyl)-4,7-dimethyl-octahydro-chromen-4-yl]-acetamide (4c).** Semisolid. $[\alpha]_D^{20} = +38.0$ (*c* 0.3). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (d, $J = 8.6$ Hz, 2H), 6.85 (d, $J = 8.6$ Hz, 2H), 5.29 (s, 1H), 4.51 (d, $J = 10.3$ Hz, 1H), 3.78 (s, 3H), 3.44 (td, $J = 10.4$, 4.2 Hz 1H), 3.07 (dd, $J = 13.8$, 1.6 Hz, 1H), 1.96 (s, 3H), 2.02–1.78 (m, 3H), 1.44 (s, 3H), 1.46–1.38 (m, 2H), 1.26–1.01 (m, 3H), 0.94 (d, 3H, $J = 6.15$ Hz), 0.94–0.92 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.0, 158.7, 134.4, 127.2, 113.6, 75.7, 75.5, 58.2, 54.0, 50.6, 42.5, 41.5, 36.6, 34.3, 31.2, 24.6, 23.0, 22.1. IR ($CHCl_3$): 3337.0, 2925.6, 2868.5, 1652.1, 1514.0 cm^{-1}. ESI (MS): $m/z = 332$ $[M + 1]^+$.

***N*-(4,7-Dimethyl-2-*p*-tolyl-octahydro-chromen-4-yl)-acetamide (3d).** White solid, m.p. 233.7 °C. $[\alpha]_D^{20} = +2.0$ (*c* 0.16). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.24 (d, $J = 8.0$ Hz, 2H), 7.11–7.09 (m, $J = 7.9$ Hz, 2H), 5.21 (s, 1H), 4.49 (dd, $J = 11.7$, 1.8 Hz, 1H), 3.46 (td, $J = 14.3$, 4.2 Hz, 1H), 2.38 (dd, $J = 13.3$, 2.1 Hz, 1H), 2.30 (s, 3H), 2.20–1.99 (m, 3H), 1.91 (s, 3H), 1.75–1.71 (m, 2H), 1.46 (s, 3H), 1.18–0.98 (m, 4H), 0.95 (d, 3H, $J = 6.4$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.4, 139.3, 136.9, 128.9, 126.0, 75.9, 75.6, 55.1, 47.7, 45.5, 41.6, 34.4, 31.3, 24.7, 23.5, 22.1, 21.1, 18.9. IR ($CHCl_3$): 3308.5, 2948.4, 2925.1, 2859.5, 1655.1, 1551.1 cm^{-1}. ESI (MS): $m/z = 338$ $[M + Na]^+$. Anal. calcd for $C_{20}H_{29}NO_2$: C 76.15; H, 9.27; N, 4.44; found: C 76.10, H 9.23, N 4.48.

***N*-(4,7-Dimethyl-2-*p*-tolyl-octahydro-chromen-4-yl)-acetamide (4d).** Gummy liquid. $[\alpha]_D^{20} = +31.0$ (*c* 0.24). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.23 (d, $J = 8.0$ Hz, 2H), 7.09 (d, $J = 7.9$ Hz, 2H), 5.31 (s, 1H), 4.52 (d, $J = 10.56$ Hz, 1H), 3.44 (td, 1H, $J = 10.4$, 4.2 Hz), 3.09 (dd, $J = 13.9$, 1.7 Hz, 1H), 2.30 (s, 3H), 2.02 (s, 3H), 2.04–1.93 (m, 2H), 1.76–1.71 (m, 2H), 1.45–1.40 (m, 1H), 1.43 (s, 3H), 1.36–1.01 (m, 4H), 0.97 (d, $J = 6.5$ Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.7, 139.4, 136.8, 128.9, 125.8, 76.7, 53.9, 50.8, 42.8, 41.6, 34.4, 31.3, 24.8, 24.6, 23.0, 22.1, 21.1. IR ($CHCl_3$): 3338.9, 2948.4, 2924.9, 2869.3, 1655.2, 1534.7 cm^{-1}. ESI (MS): $m/z = 338$ $[M + Na]^+$.

***N*-[2-(4-Isopropyl-phenyl)-4,7-dimethyl-octahydro-chromen-4-yl]-acetamide (3e).** White solid, m.p. 186.3 °C. $[\alpha]_D^{20} = +4.0$ (*c* 0.16). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 (d, $J = 6.4$ Hz, 2H), 7.17–7.14 (d, $J = 8.1$ Hz, 2H), 5.23 (s, 1H), 4.50 (dd, $J = 11.6$, 1.7 Hz, 1H), 3.42 (td, $J = 10.0$, 3.9 Hz, 1H), 2.88 (m, 1H), 2.39 (dd, $J = 13.2$, 2.0 Hz, 1H), 2.23 (m, 1H), 2.02 (m, 1H), 1.91 (s, 3H), 1.75 (m, 3H), 1.46 (s, 3H), 1.21 (d, $J = 6.8$ Hz, 6H), 1.14–0.98 (m, 4H), 0.95 (d, $J = 6.47$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.5, 148.0, 139.6, 126.3, 126.1, 75.9, 75.6, 55.2, 47.7, 45.4, 41.6, 34.4, 33.8, 31.3, 24.6, 24.06, 24.02, 23.6, 22.1, 18.9. IR ($CHCl_3$): 3319.4, 2957.4, 2926.7, 2869.2, 1652.7, 1540.2 cm^{-1}. ESI (MS): $m/z = 366$ $[M + Na]^+$. Anal. calcd for $C_{22}H_{33}NO_2$: C 76.92, H 9.68, N 4.08; found: C 76.87, H 9.64, N 4.10.

***N*-[2-(4-Isopropyl-phenyl)-4,7-dimethyl-octahydro-chromen-4-yl]-acetamide (4e).** Gummy liquid. $[\alpha]_D^{20} = +37.0$ (*c* 0.3). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.26 (d, $J = 6.2$ Hz, 2H), 7.14 (d, $J = 8.0$ Hz,

2H), 5.32 (s, 1H), 4.52 (d, 1H, $J = 10.6$ Hz), 3.44 (td, $J = 10.2$, 4.1 Hz, 1H), 3.09 (dd, $J = 13.9$, 1.4 Hz, 1H), 2.88 (m, 1H), 2.02 (s, 3H), 1.96–1.77 (m, 4H), 1.49–1.48 (m, 1H), 1.43 (s, 3H), 1.22 (d, $J = 6.9$ Hz, 6H), 1.15–0.98 (m, 4H), 0.96 (d, $J = 6.4$ Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.7, 147.9, 139.6, 126.2, 125.9, 74.8, 53.9, 50.7, 42.5, 41.5, 34.4, 33.8, 31.3, 24.8, 24.5, 24.06, 24.03, 22.9, 22.1. IR ($CHCl_3$): 3338.2, 2957.8, 2927.0, 2870.1, 1652.2, 1538.4 cm^{-1}; ESI (MS): m/z = 366 $[M + Na]^+$. HRMS (APCI) calcd for $C_{22}H_{34}NO_2$ $(M + H)^+$ requires 344.2584; found 344.2602.

***N*-[4,7-Dimethyl-2-(3-nitro-phenyl)-octahydro-chromen-4-yl]-acetamide (3f and 4f).** Gummy liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.25 (s, 1H), 8.11 (dd, $J = 8.1$, 0.9 Hz, 1H), 7.70–7.62 (m, 1H), 7.50–7.43 (m, 1H), 5.34 (s, 1H), 4.66 (d, $J = 10.2$ Hz, 1H), 3.50 (td, $J = 10.4$, 4.2 Hz, 1H), 2.46 (dd, $J = 13.2$, 1.9 Hz, 1H), 2.20–2.05 (m, 2H), 1.92 (s, 3H), 1.81–1.74 (m, 4H), 1.49 (s, 3H), 1.26–0.99 (m, 3H), 0.97 (d, $J = 6.3$ Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.8, 148.2, 144.7, 132.2, 129.2, 122.3, 121.0, 76.0, 73.7, 54.9, 47.3, 45.4, 41.4, 34.2, 31.3, 24.7, 23.4, 22.1, 18.8. IR ($CHCl_3$): 3310.1, 2927.9, 2867.9, 1655.9, 1530.9 cm^{-1}. ESI (MS): m/z = 369 $[M + Na]^+$. (δ Values given here for the major isomer present in the spectrum of the mixture of **3f** & **4f**). HRMS (APCI) calcd for $C_{19}H_{27}N_2O_4$ $(M + H)^+$ requires 347.1965; found 347.1987.

***N*-[2-(4-Chloro-phenyl)-4,7-dimethyl-octahydro-chromen-4-yl]-acetamide (3g).** White solid; m.p. 219.2 °C. $[\alpha]_D^{20}$ = +2.0 (c 0.16). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.30–7.24 (m, 4H), 5.31 (s, 1H), 4.50 (dd, $J = 11.7$, 2.0 Hz, 1H), 3.45 (td, $J = 10.4$, 4.1 Hz, 1H), 2.37 (dd, $J = 13.3$, 2.2 Hz, 1H), 2.18–2.03 (m, 2H), 1.91 (s, 3H), 1.78–1.70 (m, 3H), 1.45 (s, 3H), 1.17–0.97 (m, 4H), 0.95 (d, $J = 6.48$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.5, 140.9, 132.9, 128.3, 127.4, 77.0, 75.9, 75.0, 55.0, 47.5, 45.4, 41.5, 34.3, 31.3, 24.6, 23.5, 22.1, 18.9. IR ($CHCl_3$): 3308.1, 2926.0, 2859.3, 1650.3, 1548.0 cm^{-1}. ESI (MS): m/z = 359 $[M + Na]^+$. Anal. calcd for $C_{19}H_{26}ClNO_2$: C 67.94, 7.80, N 4.17; found: C 67.89, H 7.85, N 4.12.

***N*-[2-(4-Chloro-phenyl)-4,7-dimethyl-octahydro-chromen-4-yl]-acetamide (4g).** Gummy liquid. $[\alpha]_D^{20}$ = +12.0 (c 0.08). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.26 (s, 4H), 5.27 (s, 1H), 4.54 (dd, $J = 11.4$, 1.5 Hz, 1H), 3.47 (td, $J = 10.4$, 6.2 Hz, 1H), 3.14 (dd, $J = 13.9$, 1.6 Hz, 1H), 2.03 (s, 3H), 1.96–1.50 (m, 4H), 1.42 (s, 3H), 1.39–0.93 (m, 5H), 0.98 (d, J = 6.4 Hz, 3H). IR ($CHCl_3$): 3335.9, 2925.8, 2855.1, 1655.8, 1534.0 cm^{-1}. ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.8, 140.9, 132.7, 128.3, 127.2, 77.2, 74.8, 74.1, 53.8, 50.6, 42.6, 41.4, 34.3, 31.2, 24.8, 24.5, 22.8, 22.0; ESI (MS): m/z = 359 $[M + Na]^+$.

***N*-[2-(3,4-Dichloro-phenyl)-4,7-dimethyl-octahydro-chromen-4-yl]-acetamide (3h).** White solid. m.p. 213.2 °C. $[\alpha]_D^{20}$ = +4.0 (c 0.2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.46 (d, $J = 1.9$ Hz, 1H), 7.35 (m, 1H), 7.19 (dd, $J = 8.3$, 1.9 Hz, 1H), 5.25 (s, 1H), 4.49 (dd, $J = 11.9$, 1.9 Hz, 1H), 3.44 (td, $J = 10.3$, 4.1 Hz, 1H), 2.39 (dd, $J = 13.3$, 2.2 Hz, 1H), 2.15–2.10 (m, 3H), 1.92 (s, 3H), 1.75–1.70 (m, 2H), 1.45 (s, 3H), 1.19–1.08 (m, 4H), 0.96 (d, $J = 6.5$ Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.6, 142.7, 132.2, 131.0, 130.1, 128.0, 125.4, 75.9, 74.4, 54.9, 47.3, 45.3, 41.4, 34.3, 31.3, 24.6, 23.5, 22.1, 18.8. IR ($CHCl_3$): 3301.1, 2925.5, 2859.0, 1650.1, 1550.7 cm^{-1}. ESI (MS): m/z = 393 $[M + Na]^+$. Anal. calcd for $C_{19}H_{25}Cl_2NO_2$: C 61.62, H 6.80, N 3.78; found: C 61.58, H 6.76, N 3.84.

***N*-[2-(3,4-Dichloro-phenyl)-4,7-dimethyl-octahydro-chromen-4-yl]-acetamide (4h).** Semisolid. $[\alpha]_D^{20}$ = +24.0 (c 0.16). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45 (s, 1H), 7.42 (d, $J = 8.1$ Hz, 1H), 7.19–7.13 (m, 1H), 5.30 (s, 1H), 4.48 (d, $J = 11.3$ Hz, 1H), 3.44 (td, $J = 10.5$, 4.2 Hz, 1H), 3.17 (dd, $J = 13.8$, 1.8 Hz, 1H), 2.03 (s, 3H), 2.00–1.92 (m, 2H), 1.62 (s, 3H), 1.50–1.45 (m, 3H), 1.36–1.00 (m, 4H), 0.96 (d, $J = 6.5$ Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.6, 142.8, 127.8, 125.2, 77.0, 74.8, 73.5, 53.8, 50.5, 42.5, 41.4, 34.3, 31.2, 24.7, 24.5, 22.8, 22.0. IR ($CHCl_3$): 3327.5, 2927.1, 2868.9, 1655.7, 1537.7 cm^{-1}. ESI (MS): m/z = 393 $[M + Na]^+$.

***N*-[2-(4-Bromo-phenyl)-4,7-dimethyl-octahydro-chromen-4-yl]-acetamide (3i).** White solid; m.p. 238.0 °C. $[\alpha]_D^{20}$ = −1.0 (c 0.2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.43 (d, $J = 8.4$ Hz, 2H), 7.24 (d, $J = 8.4$ Hz, 2H), 5.30 (s, 1H), 4.48 (dd, $J = 11.7$, 1.8 Hz, 1H), 3.44 (td, $J = 10.3$, 4.1 Hz, 1H), 2.37 (dd, 1H, $J = 13.2$, 2.1 Hz), 2.17–2.03 (m, 2H), 1.91 (s, 3H), 1.75–1.70 (m, 3H), 1.46 (s, 3H), 1.18–0.98 (m, 4H), 0.95 (d, $J = 6.4$ Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.5, 141.4, 131.3, 127.8, 121.0, 77.2, 75.9, 75.0, 55.0, 47.5, 45.4, 41.5, 34.3, 31.3, 24.6, 23.5, 22.1, 18.9. IR ($CHCl_3$): 3307.4, 2948.6, 2925.6, 2858.9, 1649.8, 1549.7 cm^{-1}. ESI (MS): m/z = 403 $[M + Na]^+$. Anal. calcd for $C_{19}H_{26}BrNO_2$: C 60.00, H 6.89, N 3.68; found: C 59.96, H 6.84, N 3.73.

***N*-[2-(4-Bromo-phenyl)-4,7-dimethyl-octahydro-chromen-4-yl]-acetamide (4i).** Gummy liquid. $[\alpha]_D^{20}$ = +26.0 (c 0.2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36 (d, $J = 8.3$ Hz, 2H), 7.17–7.12 (d, $J = 8.3$ Hz, 2H), 5.21 (s, 1H), 4.45 (dd, $J = 10.3$, 1.8 Hz, 1H), 3.37 (td, $J = 10.4$, 4.2 Hz, 1H) 3.07 (dd, $J = 13.9$, 1.8 Hz, 1H) 1.96 (s, 3H), 1.89–1.38 (m, 5H), 1.34 (s, 3H), 1.31–0.90 (m, 4H), 0.88 (d, $J = 6.4$ Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.8, 141.5, 131.2, 127.8, 127.5, 120.9, 77.2, 74.8, 74.1, 53.8, 50.6, 42.6, 41.4, 34.3, 31.2, 24.8, 24.5, 22.8, 22.1. IR ($CHCl_3$): 3337.0, 2948.9, 2925.7, 2868.5, 1655.6, 1538.4 cm^{-1}. ESI (MS): m/z = 403 $[M + Na]^+$.

***N*-(2-Furan-2-yl-4,7-dimethyl-octahydro-chromen-4-yl)-acetamide (3j).** White solid, m.p. 221.2 °C. $[\alpha]_D^{20}$ = −46.0 (c 0.16). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35 (s, 1H), 6.31–6.26 (m, 2H), 5.80 (s, 1H), 4.60 (dd, $J = 10.4$, 3.5 Hz, 1H), 3.47 (td, $J = 10.4$, 4.2 Hz, 1H), 2.45–2.41 (m, 2H), 2.04–1.99 (m, 1H), 1.95 (s, 3H), 1.75–1.69 (m, 3H), 1.43 (s, 3H), 1.25–0.95 (m, 4H), 0.93 (d, $J = 6.5$ Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.6, 154.3, 142.0, 110.0, 106.7, 75.9, 69.1, 54.7, 47.6, 41.4, 34.2, 31.3, 29.6, 23.5, 22.6, 22.0, 18.7. IR ($CHCl_3$): 3356.7, 2950.8, 2925.3, 2855.4, 1668.5, 1539.6 cm^{-1}. ESI (MS): m/z = 314 $[M + Na]^+$. Anal. calcd for $C_{17}H_{25}NO_3$: C 70.07, H 8.65, N 4.81; found: C 70.01, H 8.69, N 4.76.

***N*-(2-Furan-2-yl-4,7-dimethyl-octahydro-chromen-4-yl)-acetamide (4j).** White solid; m.p. 216.0 °C. $[\alpha]_D^{20}$ = +34.0 (c 0.16). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36 (d, $J = 1.0$ Hz, 1H), 6.30–6.24 (m, 2H), 5.26 (s, 1H), 4.62 (dd, $J = 11.8$, 1.5 Hz, 1H), 3.45 (td, $J = 10.4$, 4.2 Hz, 1H), 3.12 (dd, $J = 13.8$, 1.7 Hz, 1H), 1.99 (s, 3H), 2.00–1.93 (m, 1H), 1.77–1.66 (m, 2H), 1.48 (s, 3H), 1.25–0.88 (m, 6H), 0.90 (d, $J = 6.5$ Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.5, 154.2, 142.1, 110.0, 106.8, 77.2, 68.5, 50.5, 41.3, 38.1, 34.2, 31.2, 29.7, 24.7, 24.5, 22.9, 22.0. IR ($CHCl_3$): 3338.2, 2925.7, 2854.4, 1655.4, 1535.8 cm^{-1}. ESI (MS): m/z = 314 $[M + Na]^+$.

***N*-(4,7-Dimethyl-2-thiophen-2-yl-octahydro-chromen-4-yl)-acetamide (3k).** White solid; m.p. 216.0 °C. $[\alpha]_D^{20}$ = −18.0 (c 0.16). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.21–7.20 (d, $J = 4.8$ Hz, 1H), 6.97–6.91 (m, 2H), 5.59 (s, 1H), 4.78 (d, $J = 10.5$ Hz, 1H), 3.49 (td, $J = 10.3$, 4.0 Hz, 1H), 2.59 (dd, $J = 13.1$, 1.6 Hz, 1H), 2.31 (m, 1H), 1.98 (s, 3H), 2.04–1.96 (m, 1H), 1.75–1.70 (m, 3H), 1.47 (s, 3H), 1.25–1.09 (m, 4H), 0.94 (d, $J = 6.4$ Hz, 3H). ^{13}C NMR (75 MHz,

$CDCl_3$): δ = 169.8, 145.4, 126.3, 124.5, 123.6, 76.0, 71.5, 55.0, 47.7, 45.2, 41.4, 36.6, 34.3, 31.3, 24.6, 23.5, 22.1. IR ($CHCl_3$): 3307.8, 2948.8, 2926.1, 2858.9, 1655.0, 1548.1 cm^{-1}. ESI (MS): m/z = 330 $[M + Na]^+$. Anal. calcd for $C_{17}H_{25}NO_2S$: C 66.41, H 8.20, N 4.56; found: C 66.45, H 8.16, N 4.60.

***N*-(4,7-Dimethyl-2-thiophen-2-yl-octahydro-chromen-4-yl)-acetamide (4k).** Gummy liquid. $[\alpha]_D^{20}$ = +25.0 (c 0.2). ^1H NMR (300 MHz, $CDCl_3$): δ 7.21–7.20 (m, 1H), 6.96–6.91 (m, 2H), 5.27 (s, 1H), 4.81 (d, J = 10.6 Hz, 1H), 3.47 (td, J = 10.4, 4.2 Hz, 1H), 3.25 (dd, J = 13.7, 1.4 Hz, 1H), 2.06–1.83 (m, 2H), 2.01 (s, 3H), 1.63–1.59 (m, 3H), 1.46 (s, 3H), 1.25–0.96 (m, 4H), 0.96 (d, 3H, J = 6.4 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.9, 145.4, 126.3, 124.4, 123.6, 74.9, 71.0, 53.8, 50.5, 42.1, 41.3, 36.6, 34.3, 31.2, 24.6, 22.9, 22.0. IR ($CHCl_3$): 3334.5, 2926.3, 2868.8, 1655.4, 1536.0 cm^{-1}. ESI (MS): m/z = 330 $[M + Na]^+$.

***N*-(2-Ethyl-4,7-dimethyl-octahydro-chromen-4-yl)-acetamide (3l).** White solid. m.p. 140.7 °C. $[\alpha]_D^{20}$ = −26.0 (c 0.2). ^1H NMR (300 MHz, $CDCl_3$): δ 5.22 (s,1H), 3.35–3.31 (m, 1H), 3.23–3.20 (m, 1H), 2.24 (dd, J = 11.4, 1.6 hz, 1H), 1.98–1.88 (m, 1H), 1.93 (s, 3H), 1.76–1.69 (m, 4H), 1.66–1.41 (m, 3H), 1.36 (s, 3H), 1.07–1.03 (m, 3H), 0.93 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.5, 77.2, 74.8, 54.9, 48.3, 43.3, 41.6, 34.4, 31.3, 29.0, 24.7, 23.5, 22.1, 18.9, 9.9. IR ($CHCl_3$): 3307.7, 2949.2, 2926.2, 2856.8, 1655.4, 1551.5 cm^{-1}. ESI (MS): m/z = 276 $[M + Na]^+$. Anal. calcd for $C_{15}H_{27}NO_2$: C 71.10, H 10.74, N 5.53; found: C 71.06, H 10.69, N 5.58.

***N*-(2-Ethyl-4,7-dimethyl-octahydro-chromen-4-yl)-acetamide (4l).** White solid. m.p. 136.5 °C. $[\alpha]_D^{20}$ = +35.0 (c 0.3). ^1H NMR (300 MHz, $CDCl_3$): δ 5.20 (s, 1H), 3.33 (m, 1H), 3.23 (m, 1H), 2.81 (dd, J = 13.7, 1.5 Hz, 1H), 1.97 (s, 3H), 1.96–1.80 (m, 1H), 1.74 (m, 2H), 1.49–1.43 (m, 2H), 1.41 (s, 3H), 1.20–1.01 (m, 3H), 0.96–0.88 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.6, 77.2, 74.1, 53.6, 50.9, 41.6, 40.4, 34.3, 31.2, 28.6, 24.7, 24.5, 22.9, 22.0, 9.9. IR ($CHCl_3$): 3337.0, 2926.6, 2871.9, 1650.3, 1538.0 cm^{-1}. ESI (MS): m/z = 276 $[M + Na]^+$. Anal. calcd for $C_{15}H_{27}NO_2$: C 71.10, H 10.74, N 5.53; found: C 71.15, H 10.70, N 5.48.

***N*-(4,7-Dimethyl-2-phenethyl-octahydro-chromen-4-yl)-acetamide (3m).** Gummy liquid. $[\alpha]_D^{20}$ = −26.0 (c 0.2). ^1H NMR (300 MHz, $CDCl_3$): δ 7.29–7.25 (m, 3H), 7.18–7.14 (m, 2H), 5.30 (s, 1H), 3.44 (m, 1H), 3.21 (td, J = 10.1, 3.9 Hz, 1H), 2.70 (m, 2H), 2.20 (dd, J = 12.8, 1.5 Hz, 1H), 1.98–1.90 (m, 2H), 1.93 (s, 3H), 1.88–1.64 (m, 5H), 1.31 (s, 3H), 1.21–0.92 (m, 4H), 0.94 (d, J = 6.45 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.9, 142.1, 128.4, 128.2, 125.6, 75.4, 72.4, 55.1, 48.1, 43.5, 41.6, 37.6, 34.3, 31.7, 31.3, 24.6, 24.5, 23.5, 23.4, 22.1, 18.9. IR ($CHCl_3$): 3307.3, 2925.8, 2859.0, 1650.3, 1551.1 cm^{-1}; ESI (MS): m/z = 352 $[M + Na]^+$. HRMS (APCI) calcd for $C_{21}H_{32}NO_2$ $(M + H)^+$ requires 330.2428; found 330.2450.

***N*-(4,7-Dimethyl-2-phenethyl-octahydro-chromen-4-yl)-acetamide (4m).** Gummy liquid. $[\alpha]_D^{20}$ = +36.0 (c 0.3). ^1H NMR (300 MHz, $CDCl_3$): δ 7.28–7.26 (m, 2H), 7.18–7.13 (m, 3H), 5.22 (s, 1H), 3.41 (m, 1H), 3.21–3.19 (m, 1H), 2.86 (d, J = 12.8 Hz, 1H), 2.72–2.67 (m, 2H), 1.95 (s, 3H), 1.97–1.69 (m, 6H), 1.42 (s, 3H), 1.21–1.02 (m, 5H), 0.96 (d, J = 6.45 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.8, 142.1, 128.4, 127.4, 126.4, 74.3, 73.2, 53.5, 50.6, 41.4, 40.7, 40.5, 37.2, 34.3, 31.3, 24.7, 24.5, 22.9, 22.1. IR ($CHCl_3$): 3335.9, 2925.4, 2867.5, 1650.2, 1539.7 cm^{-1}. ESI (MS): m/z = 352 $[M + Na]^+$. HRMS (APCI) calcd For $C_{21}H_{32}NO_2$ $(M + H)^+$ requires 330.2428; found 330.2453.

***N*-(2-Isopropyl-4,7-dimethyl-octahydro-chromen-4-yl)-acetamide (3n).** Gummy liquid. $[\alpha]_D^{20}$ = −26.0 (c 0.2). ^1H NMR (300 MHz, $CDCl_3$): δ 5.25 (s, 1H), 3.20–3.07 (m, 2H), 2.22 (d, J = 12.9 Hz, 1H), 1.93 (s, 3H), 1.81–1.35 (m, 7H), 1.25 (s, 3H), 1.06–0.99 (m, 3H), 0.93 (d, J = 6.6 Hz, 6H), 0.88 (d, J = 6.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.7, 78.3, 75.3, 55.2, 48.2, 41.6, 40.3, 34.4, 32.9, 31.3, 29.6, 24.6, 23.5, 22.1, 18.9, 18.3. IR ($CHCl_3$): 3306.8, 2926.8, 2856.2, 1645.0, 1553.8 cm^{-1}. ESI (MS): m/z = 290 $[M + Na]^+$, Anal. calcd for $C_{16}H_{29}NO_2$: C 71.86, H 10.93, N 5.24; found: C 71.85, H 10.91, N 5.22. HRMS (APCI) calcd for $C_{16}H_{30}NO_2$ $(M + H)^+$ requires 268.2271; found 268.2279.

***N*-(2-Cyclohexyl-4,7-dimethyl-octahydro-chromen-4-yl)-acetamide (3o).** Gummy liquid. $[\alpha]_D^{20}$ = −25.0 (c 0.2). ^1H NMR (300 MHz, $CDCl_3$): δ 5.22 (s, 1H), 3.18–3.13 (m, 2H), 2.20 (d, J = 12.4 Hz, 1H), 1.92 (s, 3H), 1.78–1.35 (m, 12H), 1.34 (s, 3H), 1.32–0.94 (m, 8H), 0.92 (d, J = 6.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.5, 77.7, 77.0, 75.3, 55.1, 48.3, 42.8, 41.6, 40.6, 34.4, 31.3, 29.2, 28.6, 26.5, 26.1, 24.7, 23.5, 22.1, 18.9. IR ($CHCl_3$): 3308.8, 2925.5, 2853.7, 1650.3, 1551.0 cm^{-1}; ESI (MS): m/z = 309 $[M + 2]^+$.

***N*-(2-Cyclohexyl-4,7-dimethyl-octahydro-chromen-4-yl)-acetamide (4o).** White solid; m.p. 120.2 °C. $[\alpha]_D^{20}$ = +37.0 (c 0.3). ^1H NMR (300 MHz, $CDCl_3$): δ 5.19 (s, 1H), 3.19–3.15 (m, 2H), 2.83 (dd, J = 13.6, 1.2 Hz,. 1H), 1.96 (s, 3H), 1.90–1.88 (m, 3H), 1.73–1.64 (m, 5H), 1.40 (s, 3H), 1.18–0.90 (m, 12H), 0.92 (d, J = 6.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.6, 77.2, 74.5, 53.7, 51.0, 42.4, 41.5, 37.6, 34.4, 31.2, 29.0, 28.9, 28.6, 26.5, 26.1, 24.7, 22.9, 22.1. IR ($CHCl_3$): 3339.2, 2926.0, 2853.1, 1654.7, 1535.5 cm^{-1}. ESI (MS): m/z = 309 $[M + 2]^+$. Anal. calcd for $C_{19}H_{33}NO_2$: C 74.22, H 10.82, N 4.56; found: C 74.18, H 10.77, N 4.60.

***N*-(4,7-Dimethyl-2-styryl-octahydro-chromen-4-yl)-acetamide (7).** White solid; m.p. 153.2 °C. $[\alpha]_D^{20}$ = −36.0 (c 0.3). ^1H NMR (300 MHz, $CDCl_3$): δ 7.36–7.18 (m, 5H), 6.60 (d, 1H, J = 16.0 Hz), 6.21 (dd, J = 16.0, 6.1 Hz, 1H), 5.32 (s, 1H), 4.18 (m, 1H), 3.38 (td, J = 10.0, 6.4 Hz, 1H), 2.34 (dd, J = 11.2, 1.9 Hz, 1H), 2.06–1.99 (m, 2H), 1.94 (s, 3H), 1.73–1.68 (m, 3H), 1.42 (s, 3H), 1.25–1.06 (m, 4H), 0.95 (d, J = 6.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.6, 136.8, 130.4, 130.1, 129.9, 128.4, 127.4, 126.4, 77.2, 75.5, 74.1, 54.8, 47.7, 43.5, 41.5, 34.3, 31.3, 24.6, 23.5, 22.1, 18.8. IR ($CHCl_3$): 2926.4, 2867.0, 1655.2, 1541.1 cm^{-1}. ESI (MS): m/z = 350 $[M + Na]^+$. Anal. calcd for $C_{21}H_{29}NO_2$: C 77.02, H 8.93, N 4.28; found: C 77.06, H 8.89, N 4.24.

***N*-(4,7-Dimethyl-2-styryl-octahydro-chromen-4-yl)-acetamide (8).** Semisolid. $[\alpha]_D^{20}$ = +37.0 (c 0.3). ^1H NMR (300 MHz, $CDCl_3$): δ 7.36–7.17 (m, 5H), 6.60 (d, J = 16.0 Hz, 1H), 6.21 (dd, J = 16.0, 5.6 Hz, 1H), 5.33 (s, 1H), 4.21 (m, 1H), 3.38 (td, J = 10.4, 4.1 Hz, 1H), 3.00 (dd, J = 3.8, 1.6 Hz, 1H), 2.01–1.90 (m, 1H), 1.93 (s, 3H), 1.78–1.45 (m, 3H), 1.44 (s, 3H), 1.41–1.00 (m, 5H), 0.96 (d, J = 6.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.9, 136.9, 130.1, 129.9, 128.4, 127.3, 126.4, 77.3, 74.3, 73.2, 53.6, 50.6, 41.4, 40.7, 34.3, 31.2, 24.7, 24.5, 23.4, 22.8, 22.1. IR ($CHCl_3$): 2927.1, 2869.7, 1656.0, 1532.2 cm^{-1}. ESI (MS): m/z = 328 $[M + 1]^+$. HRMS (APCI) calcd for $C_{21}H_{30}NO_2$ $(M + H)^+$ requires 328.2271; found 328.2282.

***N*-(4,7-Dimethyl-2-styryl-octahydro-chromen-4-yl)-acetamide (10).** Semisolid. $[\alpha]_D^{20}$ = +24.0 (c 0.16). ^1H NMR (300 MHz, $CDCl_3$): δ 7.77 (d, J = 7.2 Hz, 2H) 7.55–7.43 (m, 3H),

7.27–7.24 (m, 2H), 6.84 (d, $J = 8.5$ Hz, 2H), 6.06 (s, 1H), 4.58 (d, $J = 11.1$ Hz, 1H), 3.77 (s, 3H), 3.57 (td, $J = 10.4$, 4.1 Hz, 1H), 3.23 (d, $J = 13.6$ Hz, 1H), 2.10–2.03 (m, 2H), 1.84 (m, 1H), 1.80–1.45 (m, 2H), 1.56 (s, 3H), 1.40–0.87 (m, 4H), 0.99 (d, $J = 6.4$ Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.9, 136.9, 130.1, 129.9, 128.4, 127.3, 126.4, 77.3, 74.3, 73.2, 53.6, 50.6, 41.4, 40.7, 34.3, 31.2, 24.7, 24.5, 23.4, 22.8, 22.1. ESI (MS): $m/z = 328$ $[M + 1]^+$.

Acknowledgements

We are grateful to Department of Science & Technology, New Delhi, for financial support to this work and for fellowship of BS. We thank the Director, CSIR-NEIST, Jorhat, for his keen interest and encouragement.

References

1 Y. J. Class and P. DeShong, *Chem. Rev.*, 1995, **95**, 1843; R. D. Norcross and I. Paterson, *Chem. Rev.*, 1995, **95**, 2041; I. E. Markó and D. J. Bayston, *Synthesis*, 1996, 297; S. D. Rychnovsky, G. Yang, Y. Hu and U. D. Khire, *J. Org. Chem.*, 1997, **62**, 3022; A. B. Smith, III, P. R. Verhoest, K. P. Minbiole and M. Schelhaas, *J. Am. Chem. Soc.*, 2001, **123**, 4834; D. J. Kopecky and S. D. Rychnovsky, *J. Am. Chem. Soc.*, 2001, **123**, 8420; Y. Wang, J. Janjic and S. A. Kozmin, *J. Am. Chem. Soc.*, 2002, **124**, 13670; D. L. Aubele, S. Wan and P. E. Floreancig, *Angew. Chem., Int. Ed.*, 2005, **44**, 3485; X.-F. Yang, M. Wang, Y. Zhang and C.-J. Li, *Synlett*, 2005, 1912; X. Tian, J. J. Jaber and S. D. Rychnovsky, *J. Org. Chem.*, 2006, **71**, 3176; K. B. Bahnck and S. D. Rychnovsky, *Chem. Commun.*, 2006, 2388; K. C. Nicolaou and E. J. Sorensen, *Classics in Total Synthesis*, VCH, Weinham, 1996.

2 (*a*) E. Arundale and L. A. Mikeska, *Chem. Rev.*, 1952, **51**, 505–555; (*b*) B. B. Snider, in *Comprehensive Organic Synthesis*, ed. B. M. Trost, Pergamon Press, New York, 1991, vol. 2, p. 527; (*c*) C. Olier, M. Kaafarani, S. Gastaldi and M. P. Bertrand, *Tetrahedron*, 2010, **66**, 413–445.

3 Reviews on multi-component reactions: (*a*) L. F. Tietze and U. Beifuss, *Angew. Chem., Int. Ed.*, 1993, **32**, 131; (*b*) L. F. Tietze, *Chem. Rev.*, 1996, **96**, 115; L. F. Tietze and N. Rackelmann, *Pure Appl. Chem.*, 2004, **76**, 1967(*c*) A. Padwa, *Pure Appl. Chem.*, 2004, **76**, 1933; J. Zhu and H. Bienayme, *Multicomponent Reactions*, Wiley, Weinheim, 2005.

4 (*a*) S. D. Rychnovsky and C. R. Thomas, *Org. Lett.*, 2000, **2**, 1217; (*b*) X.-F. Yang, M. Wang, Y. Zhang and C.-J. Li, *Synlett*, 2005, 1912; (*c*) O. L. Epstein and T. Tomislav Rovis, *J. Am. Chem. Soc.*, 2006, **128**, 16480; (*d*) J. S. Yadav, B. V. Subba Reddy, T. Maity and G. G. K. S. Narayana Kumar, *Tetrahedron Lett.*, 2007, **48**, 7155; (*e*) Z. Y. Wei, J. S. Li, D. Wang and T. H. Chan, *Tetrahedron Lett.*, 1987, **28**, 3441; (*f*) F. Perron and K. F. J. Albizati, *Org. Chem.*, 1987, **52**, 4130; (*g*) Z. Y. Wei, D. Wang, J. S. Li and T. H. J. Chan, *Org. Chem.*, 1989, **54**, 5768; (*h*) L. Coppi, A. Ricci and M. J. Taddei, *Org. Chem.*, 1988, **53**, 913; (*i*) G. S. Viswanathan, J. Yang and C. J. Li, *Org. Lett.*, 1999, **1**, 993; (*j*) J. S. Yadav, B. V. Subba Reddy, G. G. K. S. Narayana Kumar and T. Swamy, *Tetrahedron Lett.*, 2007, **48**, 2205.

5 (*a*) G. H. Posner, *Chem. Rev.*, 1986, **86**, 831; (*b*) T.-L. Ho, *Tandem Organic Reactions*, Wiley-Interscience, New York, 1992; (*c*) N. Hall, *Science*, 1994, **266**, 32; (*d*) L. F. Tietze, *Chem. Rev.*, 1996, **96**, 115; (*e*) J. Montgomery, *Angew. Chem., Int. Ed.*, 2004, **43**, 3890; (*f*) E. Negishi, C. Coperet, S. Ma, S. Y. Liou and F. Liu, *Chem. Rev.*, 1996, **96**, 365; (*g*) T. Miura and M. Murakami, *Chem. Commun.*, 2007, 217; (*h*) K. Agapiou, D. F. Cauble and M. J. Krische, *J. Am. Chem. Soc.*, 2004, **126**, 4528; (*i*) K. Subburaj and J. Montgomery, *J. Am. Chem. Soc.*, 2003, **125**, 11210; (*j*) H. C. Guo and J. A. Ma, *Angew. Chem., Int. Ed.*, 2006, **45**, 354; (*k*) D. Enders, M. R. M. Huttl, C. Grondal and G. Raabe, *Nature*, 2006, **441**, 861; (*l*) S. Cabrera, J. Alemen, P. Bolze, S. Bertelsen and K. A. Jorgensen, *Angew. Chem., Int. Ed.*, 2008, **47**, 121; (*m*) O. Penon, A. Carlone, A. Mazzanti, M. Locatelli, L. Sambri, G. Bartoli and P. Melchiorre, *Chem.–Eur. J.*, 2008, **14**, 4788.

6 J. S. Yadav, Y. Jayasudhan Reddy, P. Adi Narayana Reddy and B. V. Subba Reddy, *Org. Lett.*, 2013, **15**, 546, and references cited therein.

7 (*a*) V. Michelet and J.-P. Genet, *Curr. Org. Chem.*, 2005, **9**, 405; (*b*) G. Hoefle, H. Steinmetz, K. Gerth and H. Reichenbach, *Liebigs Ann. Chem.*, 1991, 941; (*c*) Y. Suhara, Y. Yamaguchi, B. Collins, R. L. Schnaar, M. Yanagishita, J. E. K. Hildreth, I. Shimada and Y. Ichikawa, *Bioorg. Med. Chem.*, 2002, **10**, 1999; (*d*) A. Dondoni, A. Boscarato and A. Marra, *Tetrahedron: Asymmetry*, 1994, **5**, 2209; (*e*) S. Ciccotosto and M. von Itzstein, *Tetrahedron Lett.*, 1995, **36**, 5405; (*f*) S. Sabesan, S. Neira and Z. Wasserman, *Carbohydr. Res.*, 1995, **267**, 239; (*g*) B. B. Snider and N. A. Hawryluk, *Org. Lett.*, 2000, **2**, 635–638.

8 (*a*) H. Sakata and H. Yasukawa, *Jpn. Kokai Tokkyo Koho*, 2003, 42; (*b*) G. J. McGarvey, M. W. Stepanian, A. R. Bressette and M. Sabat, *Org. Lett.*, 2000, **2**, 3453.

9 E. H. Al-Mutairi, S. R. Crosby, J. Darzi, J. R. Harding, R. A. Hughes, C. D. King, T. J. Simpson, R. W. Smith and C. L. Willis, *Chem. Commun.*, 2001, 835.

10 (*a*) J. S. Yadav, B. V. Subba Reddy, G. G. K. S. Narayana Kumar and M. G. Reddy, *Tetrahedron Lett.*, 2007, **48**, 4903; (*b*) J. S. Yadav, B. V. Subba Reddy, S. Aravind, G. G. K. S. Narayana Kumar, C. Madhavi and A. C. Kunwar, *Tetrahedron*, 2008, **64**(13), 3025–3031.

11 (*a*) U. C. Reddy, B. R. Raju, E. K. P. Kumar and A. K. Saikia, *J. Org. Chem.*, 2008, **73**, 1628; (*b*) G. Sabitha, M. Bhikshapathi, S. Nayak, J. S. Yadav, R. Ravi and A. C. Kunwar, *Tetrahedron Lett.*, 2008, **49**, 5727; (*c*) J. S. Yadav, B. V. S. Reddy, S. Aravind, G. G. K. S. N. Kumar, C. Madhavi and A. C. Kunwar, *Tetrahedron*, 2008, **64**, 3025.

12 H. Banskota, Y. Tezuka, J. K. Prasain, K. Matsushige, I. Saiki and S. Kadota, *J. Nat. Prod.*, 1998, **61**, 896.

13 T. C. McKee, R. W. Fuller, C. D. Covington, J. H. Cardellina, R. J. Gulakowski, B. L. Krepps, J. B. McMahon and M. R. Boyd, *J. Nat. Prod.*, 1996, **59**, 754.

14 (*a*) V. A. Ashwood, F. Cassidy, M. C. Coldwell, J. M. Evans, T. C. Hamilton, D. R. Howlett, D. M. Smith and G. Stemp, *J. Med. Chem.*, 1990, **33**, 2667; (*b*) F. Cassidy, J. M. Evans, M. S. Hadley, A. H. Haladij, P. E. Leach and G. Stemp, *J. Med. Chem.*, 1992, **35**, 1623.

15 (*a*) K. S. Atwal, G. J. Grover, F. N. Ferrara, S. Z. Ahmed, P. G. Sleph, S. Dzwonczyk and D. E. Normandin, *J. Med. Chem.*, 1995, **38**, 1996; (*b*) K. S. Atwal, G. J. Grover, S. Z. Ahmed, F. N. Ferrara, T. W. Harper, K. S. Kim, P. G. Sleph, S. Dzwonczyk, A. D. Russell, S. Moreland, J. R. McCullough and D. E. Normandin, *J. Med. Chem.*, 1993, **36**, 3971.

16 (*a*) P. Srinivasan, P. T. Perumal and S. Raja, *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.*, 2011, **50**, 1083; (*b*) B. V. Subba Reddy, K. Ramesh, A. V. Ganesh, G. G. K. S. Narayana Kumar, J. S. Yadav and R. Gree, *Tetrahedron Lett.*, 2011, **52**, 495; (*c*) G. Sabitha, M. Bhikshapathi, S. Nayak and J. S. Yadav, *Synth. Commun.*, 2011, **41**, 8; (*d*) N. P. Selvam and P. T. Perumal, *Can. J. Chem.*, 2009, **87**, 698–705.

17 (*a*) J. S. Yadav, B. V. Subba Reddy, A. V. Ganesh and G. G. K. S. Narayan Kumar, *Tetrahedron Lett.*, 2010, **51**, 2963; (*b*) G. Baishya, B. Sarmah and N. Hazarika, *Synlett*, 2013, **24**, 1137.