Tetrahedron Letters 54 (2013) 1634–1637

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Chemo and diastereoselective conjugate addition of Grignard reagents on parthenin, a bioactive natural sesquiterpene lactone ☆

Jajula Kashanna, Paramesh Jangili, Rathod Aravind Kumar, Bethapudirr Rama Rao *

Cell Tech Laboratory–NPL, CSIR-Indian Institute of Chemical Technology, Hyderabad 500007, India

ARTICLE INFO

Article history:
Received 12 October 2012
Revised 10 December 2012
Accepted 12 December 2012
Available online 19 December 2012

Keywords:
Parthenin analogues
Grignard reagents
Mono nucleophilic addition
Chiral products
Diastereoselectivity

ABSTRACT

The conjugate addition on a natural bioactive pseudoguaianolide sesquiterpene lactone parthenin with various Grignard reagents leads to 13-C alkylated products chemo and diastereoselectively in fair overall yields. Compared with other Grignard reagents vinyl and smaller straight chain alkyl Grignard reagents gave better yields.

Organometallic reagents provide one of the most important synthetic routes to construct C–C bond in organic chemistry.[1–3] These reagents undergo addition reaction with a range of active amides, esters, thioesters, anhydrides,[4] acid chlorides[5] and α,β-unsaturated carbonyl derivatives.[6] The conjugate addition (1,4 addition) of organocopper reagents and copper(I) mediated Grignard reagents to α,β-unsaturated carbonyl derivatives is another fundamental operation in the construction of carbon–carbon bonds.[7] These addition reactions give enantioselective and regioselective products in the presence of chiral ligands.[8]Parthenin (Fig. 1) is a pseudoguaianolide sesquiterpene lactone which occurs in an exotic noxious proliferating weed *Parthenium hysterophorus Linn* (Compositae). The molecule has a central seven-membered saturated carbocyclic ring (B) which was fused to two essentially planar five membered rings-one is a carbocyclic cyclopentenone ring and the other is a heterocyclic α-methylene γ-lactone moiety (C).

The compound possesses significant anticancer,[9] antibacterial,[10] antifungal,[11] antimalarial,[12] anti-HCV,[13] allelopathic properties,[14] herbicides, antifeedant, insecticides, nematicides[15] and amoebicides.[16]

In continuation of our work on chemical transformation of parthenin herein, we report a chemo and diastereoselective conjugate addition of Grignard reagents with exocyclic double bond of parthenin (Scheme 1), which could efficiently proceed with Cu(I)I as catalyst and (*R*)-BINOL as ligand.

Cu(I)I and (*R*)-BINOL mediated Grignard reactions of parthenin with vinyl magnesium bromide in dry toluene at −78 °C afforded the formation of β-oriented product, which was isolated by column chromatography and characterized as **3a** on the basis of its spectral data.

Compound **3a** was obtained as a viscous material. Its molecular formula was determined to be $C_{17}H_{22}O_4$ from elemental analysis, and MS showed a peak at *m/z* 313[M+Na]. The structure of

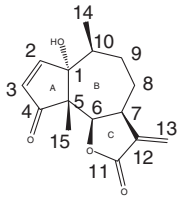
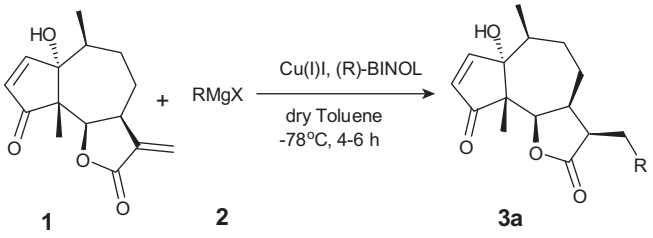


Figure 1.



Scheme 1.

☆ Part 2 in the series 'Synthetic studies on natural products'.

* Corresponding author. Tel./fax: +91 40 27160387.
E-mail address: bethapudirr@rediffmail.com (B.R. Rao).

0040-4039/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2012.12.043

Table 1
Effect of temperature on the synthesis of β-alkylated parthenin derivatives

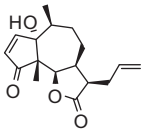
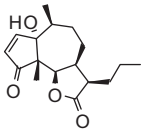
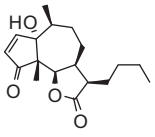
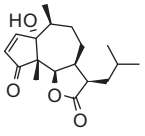
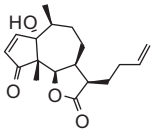
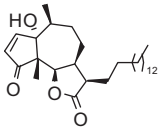
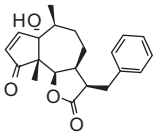
Entry[a]	Amount of Cu(I)I (mol %)	Temperature (°C)	Yield[b] (%)	dr	de[f]
1	10	0	41	74:26	48
2	20	0	46	75:25	50
3	10	−20	55	78:22	56
4	20	−20	56	80:20	60
5	10	−40	69	85:15	70
6	20	−40	72	86:14	72
7	10	−78	83	96:4	92
8	20	−78	84	95:5	90
9[c]	10	−78	86	60:40	20
10[d]	10	−78	77	86:14	72
11[e]	10	−78	80	95:5	90

[a] Reaction conditions Cu(I)I (as mentioned in column 2), BINOL (10 mol %, 0.028 g), vinyl magnesium bromide (0.458 mmol, 0.0595 g in THF), parthenin (0.100 g, 0.382 mmol in THF solution); reaction performed for 4 h in dry toluene (5 mL).
[b] Isolated yields after purification.
[c] The reaction conducted in the absence of (*R*)-BINOL.
[d] The reaction conducted with (*S*)-BINOL.
[e] Reaction performed with NEt_3.
[f] Determined by HPLC.

compound **3** was established from its IR and NMR studies including 2D experiment. In the ^{1}H NMR spectrum, the signals for H_2–13 were absent and two additional proton signals for allylic protons appeared at 5.87–5.73 (1H, m) and 5.19–5.09 (2H, m). The ^{1}H NMR and ^{13}C NMR data were assigned from COSY, HSQC and HMBC experiments allowing the identification of vinylic moiety attached at C-13 carbon. The DQF-COSY spectrum showed a correlation between H-12 and H-6. The HMBC experiment also showed that H-13 protons were correlated to the vinyl group confirming the placement of the vinyl group attached at C-13. In the NOESY experiment, Me-14 and Me-15 were correlated but they were not related to H-12 which was related to H-6, H-7. These correlations suggested β-orientation of Me-14, Me-15 and CH_2-13. Thus the structure of the product clearly settled as 13-carbon, β-oriented alkylated product of parthenin.

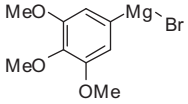
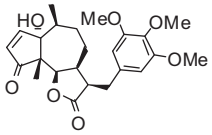
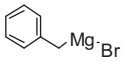
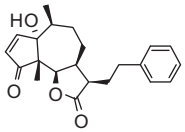
We first studied a reaction between parthenin (Fig 1) and vinyl Grignard reagent by screening the reaction conditions. In order to determine optimum conditions, we examined the influence of the reaction temperature, the reaction time and the amount of catalyst. The effect of temperature on the yields of products was studied by performing the conjugate addition reaction at 0 °C, −40 °C and −78 °C respectively (entries 2, 5, 7). The results show that lower the temperature, the more selectively the reaction could proceed without formation of any side products. Further the yield and selectivity could not be improved by the addition of Lewis base, only slight excess of Grignard reagents was required to deprotonate the BINOL. In all the reactions, the conditions were optimized for 95% conversion. It could be seen that the best result was

Table 2
Synthesis of β-alkylated parthenin derivatives

Entry[a]	Grignard reagents (2)	Product[b](3)	Time(h)	Yield[c] (%)	dr	de[d]
a			4	83	96:4	92
b			4	84	93:7	86
c			4	81	91:9	82
d			5	65	84:16	68
e			4	69	89:11	78
f			6	61	77:23	54
g			5	77	84:16	68

(*continued on next page*)

Table 2 (*continued*)

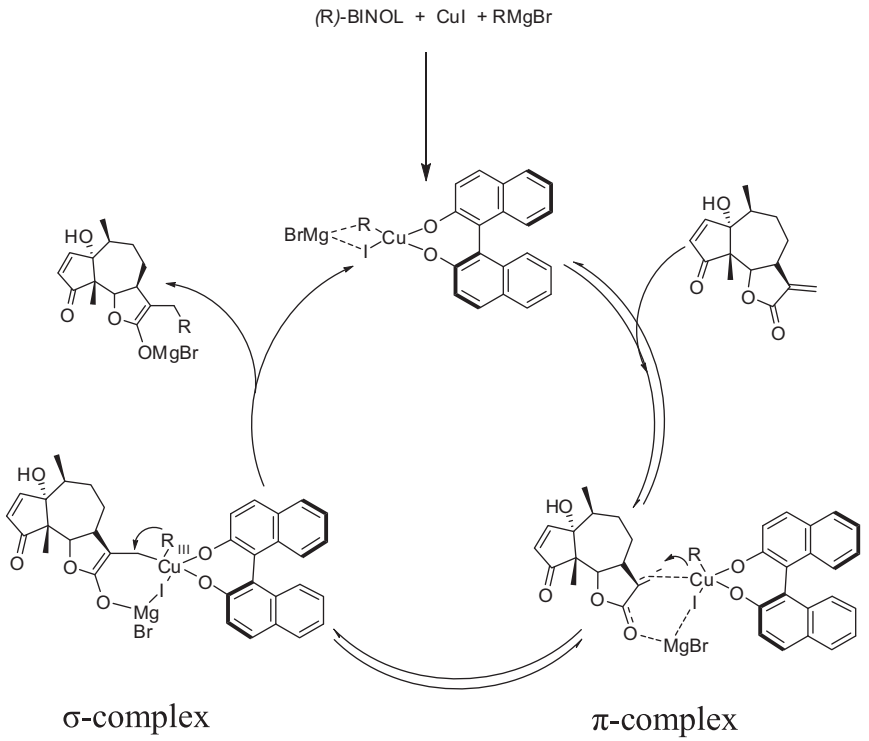
Entry[a]	Grignard reagents (2)	Product[b](3)	Time(h)	Yield[c] (%)	dr	de[d]
h			5	79	87:13	74
i			5	71	74:26	48

[a] Reaction conditions Cu(I)I (10 mol %, 0.019 g), (*R*)-BINOL (10 mol %, 0.028 g), vinyl magnesium bromide (0.458 mmol, 0.0595 g in THF), parthenin (0.100 g, 0. 382 mmol in THF solution); reaction performed for 4 h at −78 °C in dry toluene (5 mL).

[b] The structures of the products were established from their spectral (IR, ^{1}H and ^{13}C NMR, ESI-MS) data.

[c] Isolated yields after purification.

[d] Determined by HPLC.



Scheme 2.

obtained with 10 mol % of Cu(I)I and 10 mol % of (*R*)-BINOL at −78 °C (Table 1). In the absence of (*R*)-BINOL, a mixture of products (2:1) was obtained which could not be easily separated by column chromatography, while the conjugate addition of ethenyl magnesium bromide reagent can also be performed with (*S*)-BINOL leading to the α-isomer product with 72% de. However, here we were reporting the reactions only with (*R*)-BINOL.

After optimizing the conditions, we next checked the generality. Several commonly used Grignard reagents were screened (Table 2). It was observed that short chain alkyl Grignard reagent achieved higher yield than long chain alkyl Grignard reagents. As a general trend, branched aliphatic alkyl Grignard reagents gave lower yields compared to linear alkyl Grignard reagents. The vinyl, allyl and aryl Grignard reagents underwent additions smoothly and gave good yield at −78 °C.

On the basis of current information the possible mechanism for alkylation of Grignard reagents with parthenin is shown in Scheme 2.[17]

Alkyl Grignard reagents in the presence of Cu(I)I and BINOL form a complex, this complex interacts with α-methylene and oxygen atom of γ-lactone from bottom face to form a π-complex, the π-complex undergoes intramolecular rearrangement to form a Cu(III) complex, where Cu(III) forms a σ-bond with β-carbon of α-methylene γ-lactone moiety which enhances the stereopreference of enolate quenching and leads to an enolate, this enolate was quenched by proton which was approaching from bottom face to give β-isomer as exclusively major product (**3a**). Although both endocyclic and exocyclic bonds are active towards nucleophilic addition, polar conjugate addition takes place selectively across the exocyclic double bond possibly due to more steric-hindrance at endocyclic double bond and sterically unhindered exocyclic double bond. Due to these reasons the addition takes place exclusively at exocyclic double bond. In the absence of ligand the nucleophile approaches both orientation of exocyclic double bond which would be leading to a mixture of products (Table 1, entry 9).[18]

In conclusion, we have established an efficient C–C coupling at β-position of α-methylene γ-lactone moiety of parthenin with aliphatic, aromatic, vinyl and allyl Grignard reagents using Cu(1)I and (*R*)-BINOL as simple catalyst system without protecting the alcohol moiety.

Acknowledgments

The authors thank the CSIR and UGC New Delhi for the financial assistance. We are also thankful to Dr. Biswanath Das for his expert suggestions.

References and notes

1. (a) Wakefield, B. J. *Organomagnesium Methods in Organic Chemistry*; Academic press: San Diego, 1995; (b) Silverman, G. S.; Rakita, P. E. *Hand Book of Grignard Reagents*; Marcel Dekker: New York, 1996; (c) Richey, H. G., Jr. *Grignard Reagents: New Development*; Wiley: Chichester, 2000.
2. Reviews: (a) Lai, Y.-H. *Synthesis* **1981**, 585–604; (b) Eish, J. J. *Organometallics* **2002**, *21*, 5439–5463; (c) Knochel, P.; Dohle, W.; Gommermann, N.; Kneisel, F. F.; Kopp, T.; Sapountzis, I.; Vu, V. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 4302–4320.
3. Inoue, A.; Shinokubo, H.; Oshima, K. I. *Synth. Org. Chem. Jpn.* **2003**, *61*, 25–36.
4. (a) Meyer, A. I.; Comins, D. L. *Tetrahedron Lett.* **1978**, *19*, 5179–5182; (b) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815–3818; (c) Mukaiyama, T.; Araki, M.; Takei, H. *J. Am. Chem. Soc.* **1973**, *95*, 4763–4765.
5. Wang, X.-J.; Li, Z.; Xiufeng, S.; Xu, Y.; Dhileepkumar, K.; Chris, H. S. *Org. Lett.* **2005**, *7*, 5593–5595.
6. Kelly, B. G.; Gelheany, D. G. *Tetrahedron Lett.* **2002**, *43*, 887–890.
7. Dambrm, V.; Villieras, M.; Janvier, P.; Toupet, L.; Amri, H.; Lebreton, J.; Villieras, J. *Tetrahedron* **2001**, *57*, 2155–2170.
8. Fernando, L.; Adriaan, J. M.; Feringa, B. L. *Acc. Chem. Res.* **2007**, *40*, 179–188.
9. (a) Kupchan, S. M.; Eakin, M. A.; Thomas, A. M. *J. Med. Chem.* **1971**, *14*. 1147-1052; (b) Mew, D.; Balza, F.; Towers, G. H. N.; Levy, J. G. *Planta Med.* **1982**, *45*, 23–27.
10. Pieman, A. K.; Towers, G. H. N. *Biochem. Syst. Ecol.* **1983**, *11*, 321–327.
11. Pieman, A. K.; Schneider, E. F. *Biochem. Syst. Ecol.* **1983**, *21*, 307–314.
12. Hopper, M.; Kirby, G. C.; Kulkarni, M. M.; Kulkarni, S. N.; Nagasampagi, B. A.; O'Neill, M. J.; Philipson, J. D.; Rojatkar, S. R.; Warhurs, D. C. *Eur. J. Med. Chem.* **1990**, *25*, 717–723.
13. Hu, J.-N.; Patel, R.; Li, B.; Garo, E.; Hough, G. W.; Goering, M. G.; Yoo, H.-D.; O'Neil, J. M.; Fldrige, G. R. *J. Nat. Prod.* **2007**, *70*, 604–607.
14. (a) Kanchan, S. D. *Curr. Sci.* **1975**, *44*, 358–359; (b) Patil, T. M.; Hedge, B. A. *Curr. Sci.* **1988**, *57*, 1178–1181; (c) Das, B.; Das, R. *Allelopathy* **1995**, *57*, 95–101.
15. Subhendu, D.; Saxena, D. B. *Pest Manag. Sci.* **2001**, *57*, 95–101.
16. Sharma, G. L.; Bhutani, K. K. *Planta Med.* **1988**, *54*, 120–123.
17. (a) Harutyunyan, S. R.; Hartog, T. D.; Geurts, K.; Minnaard, A. J.; Feringa, B. L. *Chem. Rev.* **2008**, *108*, 2824–2852; (b) Gou, S.; Ye, Z.; Shi, L.; Qing, D.; Zhang, W.; Wang, Y. *Appl. Organomet. Chem.* **2010**, *24*, 517–522; (c) Lopez, F.; Minnard, A. J.; Feringa, B. L. *Acc. Chem. Res.* **2007**, *40*, 188–197.
18. *General experimental procedure for the preparation of β-alkylated parthenin derivatives (**3a–3i**)*: Cu(I)I (10 mol %, 0.019 g) was taken in an oven-dried 25 ml two necked RB. It is cooled to −78 °C and, (*R*)-BINOL (10 mol %, 0.028 g) dissolve in dry toluene (5 mL) and vinyl magnesium bromide (0.458 mmol, 0.0595 g in THF) were added under nitrogen atmosphere, stirred for 5 min,— Then parthenin (0.100 g, 0. 382 mmol in THF) was added and stirred for 4 h. The reaction mixture was concentrated in vacuo and extracted with EtOAc (3 × 30 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue on purification by column chromatography (ethyl acetate/hexane, 40:60) afforded pure products.
The spectral and analytical data of some representative products are given below:
*13β-ethenyl-11,13-dihydroparthenin (**3a**).*
IR: 3451, 2960, 2875, 1664, 1620, 1380, 1200 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.49 (1H, d, *J* = 6.0 Hz), 6.19 (1H, d, *J* = 6.0 Hz), 5.87–5.73 (1H, m), 5.19–5.09 (2H, dd), 4.91 (1H, d, *J* = 8.0 Hz), 2.80–2.70 (H, m), 2.55–2.27 (3H, m), 2.17–2.01 (3H, m), 1.68–1.59 (2H, m), 1.33 (3H, s), 1.13 (3H, d, *J* = 8.0 Hz); ^{13}CNMR (50 MHz, $CDCl_3$): δ 210.5, 178.9, 162.5, 134.0132.0, 118.5, 84.9, 78.8, 59.2, 47.8, 45.5, 40.6, 35.5, 30.4, 27.0, 18.6, 17.0; ESIMS: *m*/*z* 291 $[M+H]^+$. Anal. calcd for $C_{17}H_{22}O_4$: C, 70.32; H, 7.58%; found: C, 70.18; H, 7.64.
*13β-isopropyl-11,13-dihydroparthenin (**3d**).*
IR: 3439, 2924, 2853, 1757, 1717, 1640, 1453; ^1H NMR (200 MHz, $CDCl_3$): δ 7.55 (1H, d, *J* = 6.0 Hz), 6.14 (1H, d, *J* = 6.0 Hz), 4.87 (1H, d, *J* = 8.0 Hz), 2.71–2.60 (1H, m), 2.40–2.29 (1H, m), 2.20–2.05 (2H, m), 1.90–1.50 (6H, m), 1.31–1.20 (3H, m), 1.12 (3H, d, *J* = 8.0 Hz), 0.92 (6H, d, *J* = 7.0 Hz): ^{13}CNMR (50 MHz, $CDCl_3$): δ 208, 179.0, 158.2, 138, 84.9, 78.0, 69.1, 54.0. 47.3, 44.5, 41.0, 30.2, 28.4, 25.6, 24.2, 18.5, 17.0; ESIMS: *m*/*z* 307 $[M+H]^+$. Anal. calcd for $C_{18}H_{26}O_4$: C, 71.05; H, 8.49%; found: C, 70.93; H, 8.55.
*13β-tetradecanyl-11,13-dihydroparthenin (**3f**).*
IR: 3438, 2921, 2855, 1748, 1716, 1639, 1455; ^1H NMR (200 MHz, $CDCl_3$): δ 7.46 (1H, d, *J* = 6.0 Hz), 6.2 (1H, d, *J* = 6.0 Hz), 4.90 (1H, d, *J* = 8.0 Hz), 2.77–2.70 (1H, m), 2.30–2.19 (3H, m,), 2.18–1.90 (3H, m), 1.5–1.25 (33H, m), 1.14 (3H, d, *J* = 8.0 Hz): ^{13}CNMR (50 MHz, $CDCl_3$): δ 209.2, 179.4, 161.0, 134.6, 83.9, 78.6, 59.4, 44.9, 42.0, 40.2, 30.1, 29.0, 27.8, 17.6, 18.5, 17.1; ESIMS: *m*/*z* 450 $[M+H]^+$. Anal. calc for $C_{29}H_{37}O_4$: C, 77.50; H, 8.24%; found: C, 77.38; H, 8.30.
*13β-phenyl-11,13-dihydroparthenin (**3g**).*
IR: 3444, 2925, 2856, 1757, 1718, 1639, 1451; ^1H NMR (200 MHz, $CDCl_3$): δ 7.47 (1H, d, *J* = 6.0 Hz), 7.30 (2H, d, *J* = 8.0 Hz), 7.25 (2H, d, *J* = 8.0 Hz), 7.20 (1H, dd), 6.21 (1H, d, *J* = 6.0 Hz), 4.78 (1H, d, *J* = 8.0 Hz), 3.10–3.05(1H, m), 3.00–2.92 (2H, m), 2.85–2.81 (1H, m), 2.34–2.24 (1H, m), 2.06–1.88 (2H, m), 1.80–1.55 (2H, m), 1.34 (3H, s), 1.11 (3H, d, *J* = 8.0 Hz); ^{13}CNMR (50 MHz, $CDCl_3$): δ 204.2, 187.1, 167, 142.1, 132.5, 130.0, 128.0, 127.2, 81.2, 78.2, 59.1, 50.1. 46.7, 41.6, 33.2, 31.9, 29.8, 19.1, 18.4; ESIMS: *m*/*z* 341 $[M+H]^+$. Anal. calc for $C_{21}H_{24}O_4$: C, 74.11; H, 7.05%; found: C, 73.99; H, 7.11.