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Chemistry of andrographolide: formation of novel di-spiropyrrolidino and di-spiropyrrolizidino-oxindole adducts via one-pot three-component [3+2] azomethine ylide cycloaddition

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ABSTRACT

A facile synthesis of novel di-spiro compounds has been achieved via 1,3-dipolar cycloaddition of azomethine ylides generated in situ from isatin derivatives and sarcosine to the conjugated double bond of andrographolide. When the amino acid was changed from sarcosine to L-proline, the product formation took a different course as determined by 2D NMR and X-ray crystallographic analysis.

1. Introduction

Andrographolide, the major labdane diterpene constituent of *Andrographis paniculata* (family Acanthaceae), is used extensively in the traditional system of medicine in south east Asia since antiquity.[1,2] Extracts of the plant and its constituents are reported to exhibit a wide range of biological activities of therapeutic importance that include hepatoprotective,[3] antimalarial,[4] antibacterial,[5] anti-inflammatory,[6] antithrombotic,[7] immune stimulant,[8] and anticancer.[9] Reports on the synthesis of andrographolide derivatives for modification of the biological activities are available in the literature. Derivatizations were based on the reaction of hydroxyl groups, epoxidation of the 8,17 double bond, and acidic rearrangement involving the two double bonds.[10–12] Nanduri et al. reported the synthesis of some oxindole, thiazolidinone, and rhodanine analogues of andrographolide by oxidative cleavage of Δ^{12}-bond followed by Knoevenagel condensation and/or Wittig olefination.[13] Bio-evaluation of the derivatives have shown anticancer, α-glucosidase inhibitory[14] as also TNF-α and IL-6 expression inhibitory activity.[12] Selective reduction of the conjugated double bond by sodium borohydride and Michael type addition of glutathione involving Δ^{12}-bond of andrographolide are also reported.[15,16]

The [3+2] azomethine ylide cycloaddition at electron-deficient conjugated double bonds is one of the important methods for the construction of heterocyclic five-membered rings, for example, pyrrolidines, which are used as important building blocks in the synthesis of natural products as well as pharmaceuticals.[17–19] The pyrrolidine-2-spiro-3′-oxindole ring system is found in a variety of oxindole alkaloids, for example, horsfiline,[20] spirotryprostatin[21,22]. Aldose reductase and poliovirus or rhinovirus 3C-proteinase inhibitory activities were observed in some spirooxindole analogues.[23] This type of ring system can be prepared by [3+2] cycloaddition of azomethine ylides generated in situ from isatins and secondary α-amino acids.[24] Presuming that incorporation of isatins and α-amino acids in andrographolide might generate some bioactive molecules, we attempted to effect the hitherto unknown dipolar cycloaddition at the 12,13 double bond of andrographolide, without affecting the rest of the molecule. In this Letter we wish to present the novel synthesis of some dispiropyrrolidino- and di-spiropyrrolizidino-oxindole adducts of andrographolide by reacting with isatins and secondary α-amino acids.

2. Results and discussion

The reactions/cycloadditions were performed by in situ generation of the azomethine ylides from isatin analogues and α-amino acids such as sarcosine (Scheme 1) and proline (Scheme 2).

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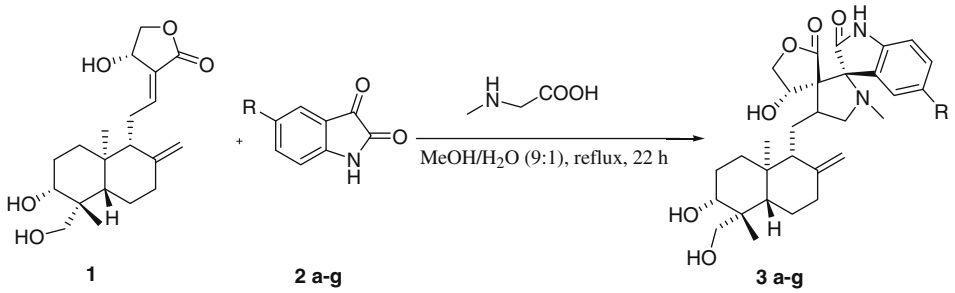
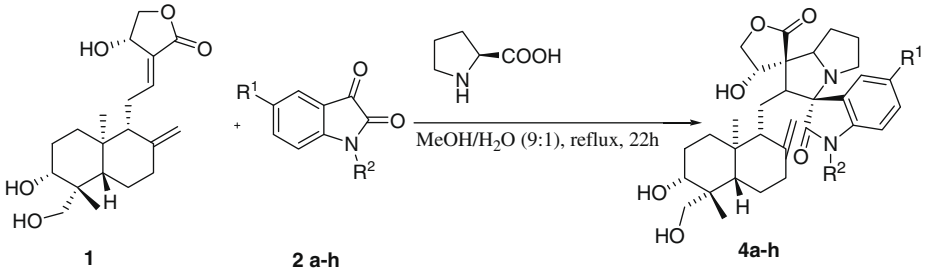


Scheme 1. Synthesis of dispiro pyrrolidino oxindolo andrographolide adducts.



Scheme 2. Synthesis of dispiropyrrolizidino-oxindolo andrographolide adducts.

Carried out under reflux (~80 °C) in methanol–water (9:1), the reaction took around 20–22 h to produce **3a–g** and **4a–h** in good yield (Tables 1 and 2).[25]

The products were characterized mainly from spectral studies. Mass spectral analysis of the products testified to the success of the cycloaddition reaction in all the cases. Preliminary examination of the NMR spectral data also provided supporting evidence.[26,27] As would be expected, the signals for the fused six-membered ring fragments of andrographolide remained virtually unaltered in the spectra of the products (andrographolide numbering has been maintained for the basic skeleton for ease in correlation). But the chemical shifts for the nuclei belonging to the α,β-unsaturated-γ-lactone part of **1** were distinctly perturbed, with C_{12} and C_{13} suffering profound alteration in the resonance position. Curiously, the shifts followed somewhat different paths for the sarcosine series (**3a–g**) and the proline series (**4a–h**) of products. As the C_{13} signal was more downfield in the former and C_{12} signal was more downfield in the latter, it appeared that the addition might have taken opposite courses depending on the amino acid used; isatin, which contributes two α substituents in the product to the neighboring carbon, appeared likely to add from the C_{13} end in sarcosine series but from the C_{12} end in the proline series. This was also borne out by the 2D NMR spectral correlations for the representative compound **3a** for the sarcosine series (Fig. 1). The crucial evidence in support of the orientation came from the observed COSY relationship between the signals for H-12 (δ 2.90) and the CH_2N– protons

Table 1
Yields of **3a–g**

Entry	R	Product (**3a–g**)	Yield[a] (%)
1	H	**3a**	60
2	Me	**3b**	62
3	Cl	**3c**	61
4	I	**3d**	60
5	F	**3e**	64
6	OMe	**3f**	62
7	Br	**3g**	59

[a] Isolated yield.

Table 2
Yields of **4a–h**

Entry	R^1	R^2	Product (**4a–h**)	Yield[a] (%)
1	H	H	**4a**	60
2	Me	H	**4b**	61
3	Cl	H	**4c**	59
4	I	H	**4d**	58
5	F	H	**4e**	60
6	OMe	H	**4f**	60
7	Br	H	**4g**	58
8	H	Me	**4h**	64

[a] Isolated yield.

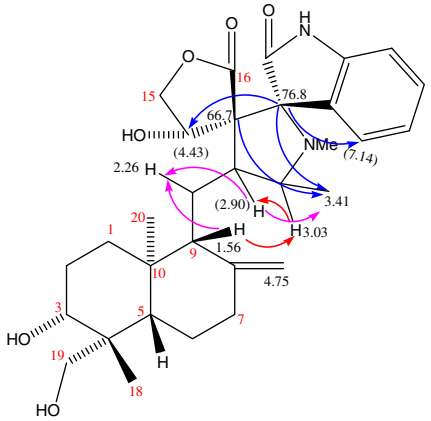


Figure 1. Important correlations of **3a** [HMBC (C ⟶ H), COSY ( ), NOESY ( )].

(δ 3.03, 3.41). The δ 3.03 signal showed clean splitting pattern with *J* values large enough (*J* = 6 Hz) to identify H-12 as a neighboring proton. Considering the Newman projection for the C_9–C_{11} bond, the heterocyclic fragment is likely to adopt the orientation shown to avoid steric interaction with the six-membered ring residues.

As the 9β-H signal was correlated in the NOESY spectrum with the 12-H signal, the latter must be β-oriented as shown. The olefinic proton in andrographolide is known to be cis oriented with respect to the carbonyl group; the latter should therefore be β to the newly generated pyrrolidine ring. On mechanistic consideration again, the lactam carbonyl will prefer to be α-oriented to avoid dipolar repulsion with the lactone carbonyl. However, no supportive evidence was forthcoming from the NOESY spectrum (the δ 7.14 ppm aromatic proton peak showed no correlation with any aliphatic proton signal).

The assignment of proton and carbon signals for **4a–h**, where proline was used as the amino acid, showed some interesting trends (Fig. 2). The NMR spectrum of compound **4h** showed HMBC correlation between the peak for 12-H and C-2 (lactam carbonyl), C-3 (spiro centre), and C-4a (ring junction) of isatin indicating its attachment at C-12 of andrographolide.

In support, correlation of H-14 signal with C-2 signal of proline and C-12 signal indicated the attachment of the other part of the dipole at C-13, in the reverse direction to that in the sarcosine series.

It is pertinent to note that the exomethylene protons (2H-17) of **4h** resonated at δ 4.53 and 3.69, differing significantly from those of **3a** where both appeared at δ 4.75. This suggested that one of the protons (δ 3.69) of exomethylene group was in the shielding zone to the lactam carbonyl group or the aromatic ring of oxindole.[28] The NOESY correlation between H-12 and H-9 signals clearly indicated the β orientation of H-12 as in case of **3a**. From this spectroscopic analysis, **4h** was concluded to be a dispiropyrrolizidino-oxindole adduct of andrographolide with a reverse regiochemistry compared to the **3** series. This was finally confirmed by its single crystal X-ray crystallographic analysis.

A SCHAKAL representation[29] of the molecular structure of **4h**, showing also the atomic numbering scheme, is given in Figure 3.

Bond lengths and angles are as expected. The hetero bonding geometry in the tetrahydrofuranone and oxindole fragments are as observed before.[30–32] The oxindole fragment is expectedly planar. Of the non-planar rings, the six-membered rings are in chair conformations while the five-membered rings have envelope conformations. The six-membered rings and the oxindole fragment are in almost parallel orientation.

The three O–H groups are donors of hydrogen bonds, two of them, O4–H4···O5 and O2–H2···O6, are intramolecular, while the intermolecular hydrogen bond O5–H5···O4 relates two molecules via the screw axis in *b*-direction.

The cycloaddition reactions proceeded in a chemoselective fashion as only one of the two double bonds present in the dipolarophile took part. The reactions also appear to occur in a diastereoselective manner, though the presence of minor stereoisomers cannot be ruled out. Change in amino acid from sarcosine to proline altered the course of the reaction and yielded products with reverse regiochemistry as appeared recently in the literature.[33] The role of the –NH of isatin was not of much importance as the use of *N*-methyl isatin showed virtually no change in the formation of product.[34] Based on the literature reports the mechanism involves the formation of an intermediate oxazolidinone. In the presence of the dipolarophile (andrographolide), it undergoes loss of CO_2 via a stereospecific 1,3-cycloreversion forming the azomethine ylide, which undergoes 1,3-dipolar cycloaddition to give the dispiro compound.[35] This is the first report of one-pot three-component [3+2] azomethine ylide cycloaddition to andrographolide.

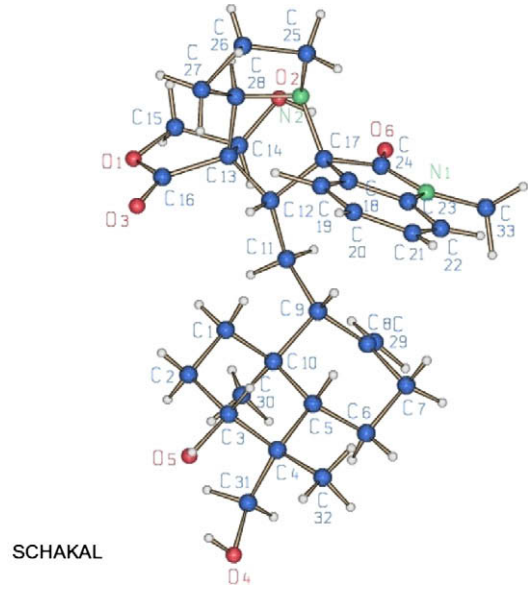


Figure 3. SCHAKAL representations[29] of **4h**.

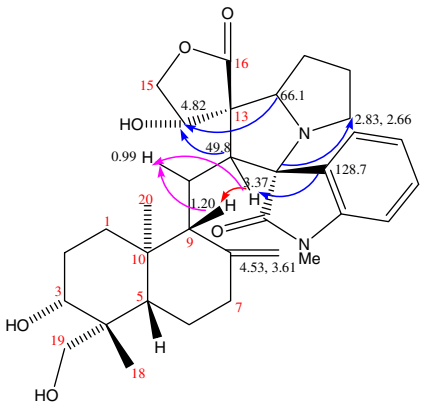


Figure 2. Important correlations of 4 h [HMBC (C ⟶ H), COSY (⟶), NOESY (⟶)].

3. Conclusions

In conclusion, a facile, atom-economic synthesis of novel dispiro compounds has been achieved via 1,3-dipolar cycloaddition of azomethine ylides generated from isatin and sarcosine to Δ^{12} of andrographolide. When the amino acid was changed from sarcosine to proline, the product formation took a different course, as determined by 2D NMR and confirmed by X-ray crystallographic analysis.

Acknowledgments

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Supplementary data

^{1}H and ^{13}C NMR spectra of all new compounds associated with this article can be found in the online version. Crystallographic data in CIF format are available free of charge via the Internet at CCDC 725167. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cam-

bridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; or deposit@ccdc.cam.ac.uk). Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.01.052.

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25. *General method of preparation*: A mixture of **1** (0.58 mmol, 200 mg), isatin (0.6 mmol, 90 mg), and proline (0.61 mmol, 70 mg) or sarcosine (0.61 mmol, 54 mg) was dissolved in methanol–water (90:10) and heated to reflux for almost 24 h. After completion of the reaction as evident from TLC, the solvent was removed in vacuum. The crude product was subjected to column chromatography using chloroform–methanol (0.5% methanol in chloroform) as eluant. The product was crystallized from acetonitrile–benzene mixture.
26. *Compound* **3a**: Obtained as white solid, mp 234–236 °C; IR (KBr, ν_{max}) 3374, 2938, 2851, 1724, 1619, 1471 cm^{-1}; ^1H NMR (CD_3OD) δ 7.30 (1H, dt, J = 1.2, 7.8 Hz), 7.14 (1H, d, J = 7.2 Hz), 7.01 (1H, dt, J = 0.6, 7.8 Hz), 6.85 (1H, d, J = 7.8 Hz), 4.82 (2H, d, J = 12 Hz), 4.43 (1H, d, J = 2.4 Hz), 4.13 (1H, d, J = 11.4 Hz), 3.76 (1H, d, J = 10.2 Hz), 3.41 (2H, m), 3.35 (1H, m), 3.18 (1H, dd, J = 2.4, 10.2 Hz), 3.03 (1H, dd, J = 6.0, 9.0 Hz), 2.90 (1H, m), 2.53 (1H, m), 2.41 (1H, m), 2.26 (1H, t, J = 12.6 Hz), 2.04 (1H, m), 2.01 (1H, m), 1.97 (3H, s), 1.82 (3H, m), 1.56 (1H, d, J = 11.4 Hz), 1.34 (1H, m), 1.28 (2H, m), 1.22 (3H, s), 0.69 (3H, s); ^{13}C NMR (CD_3OD) δ 15.9 ($-CH_3$), 23.6 ($-CH_3$), 25.6 ($-CH_2$), 26.3 ($-CH_2$), 29.3 ($-CH_2$), 35.7 ($-CH_3$), 38.6 ($-CH_2$), 39.7 ($-CH_2$), 40.4 (–CH), 40.5 (–C), 43.9 (–C), 56.3 (–CH), 57.0 (–CH), 61.1 ($-CH_2$), 65.3 ($-CH_2$), 66.7 (–C), 73.3 (–CH), 75.4 ($-CH_2$), 76.8 (–C), 81.4 (–CH), 108.6 ($-CH_2$), 111.0 (–CH), 123.9 (–CH), 126.9 (–CH), 127.0 (–C), 131.5 (–CH), 144.2 (–C), 148.7 (–C), 179.1 (–C=O), 180.7 (–C=O); MS (ESI-MS, positive ion) m/z 525 $[M+H]^+$, 547 $[M+Na]^+$; HRMS m/z 525.2943 $[M+H]^+$ [calcd 525.2965].
27. *Compound* **4h**: Obtained as white solid, mp 208–210 °C; IR (KBr, ν_{max}) 3321, 2950, 2885, 1771, 1700, 1610, 1469 cm^{-1}; ^1H NMR (CD_3OD) δ 7.47 (1H, m), 7.25 (2H, m), 7.10 (1H, d, J = 7.8 Hz), 4.82 (1H, dd, J = 8.4, 9 Hz), 4.61 (1H, t, J = 7.8 Hz), 4.53 (1H, s), 4.17 (1H, dd, J = 6.6, 9 Hz), 3.97 (1H, d, J = 11.4 Hz), 3.94 (1H, t, J = 9 Hz), 3.69 (1H, s), 3.37 (1H, dd, J = 4.2, 10.2 Hz), 3.32 (1H, m), 3.24 (1H, d, J = 11.4 Hz), 3.19 (3H, s), 2.83 (1H, m), 2.66 (1H, m), 2.19 (1H, m), 1.93 (1H, m), 1.71 (7H, m), 1.57 (2H, m), 1.20 (1H, m), 1.15 (1H, m), 1.13 (1H, m), 1.12 (3H, s), 0.99 (1H, m), 0.93 (1H, dd, J = 2.4, 12.6 Hz), 0.43 (3H, s); ^{13}C NMR (CD_3OD) δ 15.0 ($-CH_3$), 21.1 ($-CH_2$), 23.5 ($-CH_3$), 25.6 ($-CH_2$), 26.3 ($-CH_2$), 26.8 ($-CH_3$), 29.0 ($-CH_2$), 29.6 ($-CH_2$), 38.1 ($-CH_2$), 39.3 ($-CH_2$), 40.8 (–C), 43.7 (–C), 49.8 (–CH), 50.2 ($-CH_2$), 53.9 (–CH), 56.9 (–CH), 58.0 (–C), 65.0 ($-CH_2$), 66.1 (–CH), 68.5 (–CH), 70.5 ($-CH_2$), 77.2 (–C), 80.9 (–CH), 107.1 ($-CH_2$), 110.9 (–CH), 124.5 (–CH), 127.4 (–CH), 128.7 (–C), 131.5 (–CH), 145.6 (–C), 148.5 (–C), 179.6 (–C), 181.6 (–C); MS (ESI-MS, positive ion) m/z 565 $[M+H]^+$, 587 $[M+Na]^+$; HRMS m/z 565.3285 $[M+H]^+$ [calcd 565.3278], 587.3078 $[M+Na]^+$ [calcd 587.3097].
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