2007

Syntheses of spiro[cyclopropane-1,3'-oxindole]-2-carboxylic acid and cyclopropa[c]quinoline-7b-carboxylic acid and their derivatives

Sarah Yong
University of Wollongong, sry02@uow.edu.au

Alison T. Ung
University of Wollongong, alison_ung@uow.edu.au

Stephen G. Pyne
University of Wollongong, spyne@uow.edu.au

Brian W. Skelton
University of Western Australia

Allan H. White
University of Western Australia

Publication Details

Yong, S. R., Ung, A. T., Pyne, S. G., Skelton, B. W. & White, A. H. (2007). Syntheses of spiro[cyclopropane-1,3'-oxindole]-2-carboxylic acid and cyclopropa[*c*]quinoline-7b-carboxylic acid and their derivatives. Tetrahedron, 63 (5), 1191-1199.

Syntheses of spiro[cyclopropane-1,3'-oxindole]-2-carboxylic acid and cyclopropa[c]quinoline-7b-carboxylic acid and their derivatives

Abstract
The synthesis of spiro[cyclopropane-1,3′-oxindole]-2-carboxylic acid, including novel 3-(2- and 3-pyridyl)-substituted analogues and the novel cyclopropa[*c*]quinoline-7b-carboxylic acid and their ester and amide derivatives is described. These syntheses involve diastereoselective cyclopropanation reactions of methyl 2-(2-nitrophenyl)acrylate and (3*E*)-(pyridin-2-ylmethylene)- and (3*E*)-(pyridin-3-ylmethylene)-1,3-dihydro-2*H*-indol-2-one with ethyl (dimethyl sulfuranylidene) acetate (EDSA). The synthesis of methyl cyclopropa[*c*]quinoline-7b-carboxylate involves a regioselective reductive cyclization of a nitro-diester precursor. The relative stereochemistry of key compounds has been determined by single-crystal X-ray structural analysis.

Keywords
Syntheses, spiro, cyclopropane, oxindole, carboxylic, acid, cyclopropa, quinoline, carboxylic, acid, their, derivatives, CMMB

Publication Details
Yong, S. R., Ung, A. T., Pyne, S. G., Skelton, B. W. & White, A. H. (2007). Syntheses of spiro[cyclopropane-1,3'-oxindole]-2-carboxylic acid and cyclopropa[*c*]quinoline-7b-carboxylic acid and their derivatives. Tetrahedron, 63 (5), 1191-1199.

Synthesis of spiro[cyclopropane-1,3'oxindole]-2-carboxylic acid and cyclopropa[c]quinoline-7b-carboxylic acid derivatives

Sarah R. Yong[a], Alison T. Ung[a]*, Stephen G. Pyne[a]*,
Brian W. Skelton[b] and Allan H. White[b]

[a]*Department of Chemistry, University of Wollongong, Wollongong, New South Wales, 2522, Australia*
[b]*Department of Chemistry, University of Western Australia, Crawley, Western Australia, 6009, Australia.*

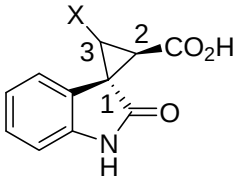
Abstract: The phosphine-catalysed [3+2]-cycloaddition of the 2-methylene γ-lactams **4** and **5** and the acrylate **6** with the ylides derived from the ethyl ester, the amide or the chiral camphor sultam derivative of 2-butynoic acid (**7a-c**) give directly, or indirectly after reductive cyclization, spiro-heterocyclic products. The acid **32** underwent Curtius rearrangement and then acid hydrolysis to give two novel spiro-cyclic ketones, **41** and **42**.

Key words: cyclopropanation, sulfur ylide, spirocyclic compounds, oxindole

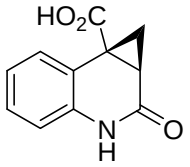
Corresponding authors: e-mail: aung@uow.edu.au; spyne@uow.edu.au

1. Introduction

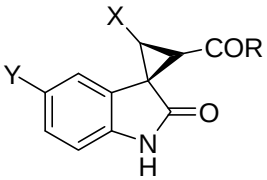
3'-Spirocyclo-oxindoles, of synthetic or natural origin, have a range of biological activities.[1-3] As part of a medicinal chemistry project we have been focusing on the synthesis of novel 3'-spirocyclo-oxindoles and we recently reported the preparation of 3'-spiropentacyclo-oxindoles derivatives using phosphine-catalyzed [3+2]-cycloaddition reactions.[4] As an extension of this project we required the synthesis of 3'-spirocyclopropyloxindole-2-carboxylic acid **1** and cyclopropa[c]quinoline-7b-carboxylic acid **3** and their ester and benzamide derivatives and the 3-(2- and 3-pyridyl)-substituted analogues (**2**) of **1**.

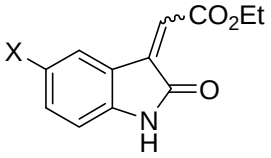


1, X = H
2, X = 2- or 3-pyridiyl



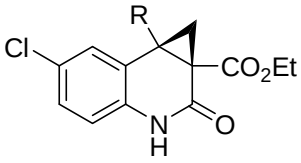
3





4; R = OH, O-alkyl or NHR; X = H, Y = H or Br
5; R = OEt; X = Ph, Y = H
6; R = Ph; X = Ar; Y = H
7; R = Ph; X = H; Y = H

8



9; R = alkyl

During the course of this project He *et al.*[4] reported that some ester and amide derivatives of the 5'-bromo-3'-spirocyclopropyloxindole-2-carboxylic acid **4** (R = OH, Y = Br) were potent HIV-1 non-nucleoside reverse transcriptase inhibitors (NNRTIs) on both wild-type and drug resistant mutant viruses. The ethyl ester of compound **4** was prepared from the 3-carboethoxymethylene derivative of 5-bromoisatin (**8**, R = Br) by treatment with diazomethane to generate the cyclopropanated product, via its diazo intermediate. Similar reactions have been utilized earlier to prepare 2-substituted-3'-spirocyclopropyloxindole-2-carboxylic esters, however extension of these reactions to prepare 3-phenyl-3'-spirocyclopropyloxindole-2-carboxylic esters **5** using phenyldiazomethane were unsuccessful.[5] Interestingly, when diphenyldiazomethane was employed the desired 3,3-diphenyl-3'-spirocyclopropyloxindole-2-carboxylic ester was obtained.[6] In the same year Shanmugam reported the synthesis of *N*-alkyl derivatives of **4** (R = O-alkyl, X = H, Y = H or Br) employing a reductive cyclization reaction to prepare the cyclopropane ring.[7] Indeed prior to the work disclosed here, no methods were available to prepare 3-aryl-3'-spirocyclopropyloxindole-2-carboxylic esters, including the desired 3-(2- and 3-pyridyl)-substituted analogues **2**. Earlier work by Croce,[8] however, showed that the related phenyl ketone derivatives, **6** and **7** could be prepared from the reaction of dimethylsulfonium phenacylide ($Me_2S(+)CH(-)COPh$) with **8** (R = H) or 3-methylene-indoline-2-one, respectively. The former products were formed as a mixture (1.5-3.5 : 1) of diastereomers.

In 2006 He *et al*.[9] also disclosed that derivatives of the ethyl cyclopropa[c]quinoline-1c-carboxylate **9**, closely related to our target structure **3**, also had potent HIV antiviral activities as NNRTIs.

We report here our own efforts for preparing 3'-spirocyclopropyloxindole derivatives related to **1** and a method of preparing for the first time 3-aryl-substituted analogues **2** (X = 2- or 3-pyridyl) using stabilized sulfur ylides. Furthermore, we report an efficient and highly diastereoselective synthesis of cyclopropa[c]quinoline-7b-carboxylic acid **3**, a new isomer of He's compound **9**.

2. Results and Discussion

The synthesis of the corresponding esters of **1** and **3**, **13** and **12**, respectively (Scheme 1) could in principle be achieved by regioselective reductive cyclization reactions of the nitro diester **11**. Based on literature precedent of related but non-cyclopropanated nitro diesters, cyclization should favour formation of a quinoline ring system over an oxindole ring structure.[10,11] However, at the onset of this study, the effect of the cyclopropane moiety in **11** on the regioselectivity of such a reductive cyclization reaction was not certain. The nitro-diester **11** was prepared in 80 % yield in a completely diastereoselective fashion by treatment of the acrylate **4**[4, 12] with ethyl (dimethyl sulfuranylidene) acetate (EDSA, 1.5 equiv) in anhydrous toluene for 20 h at rt. Single X-ray crystallographic analysis of **11** showed that the two polar ester groups had a *trans*-stereochemical relationship (Figure 1). This stereochemical outcome was expected based on literature precedent of related reactions.[13]

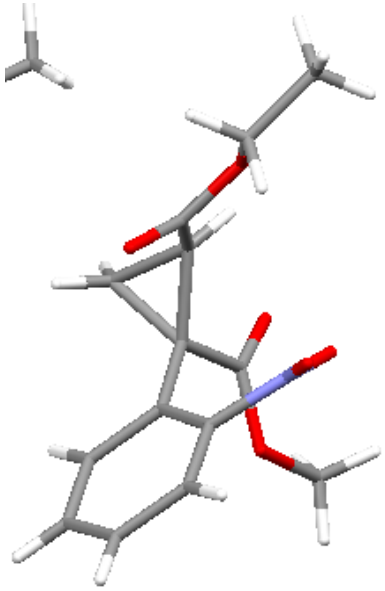
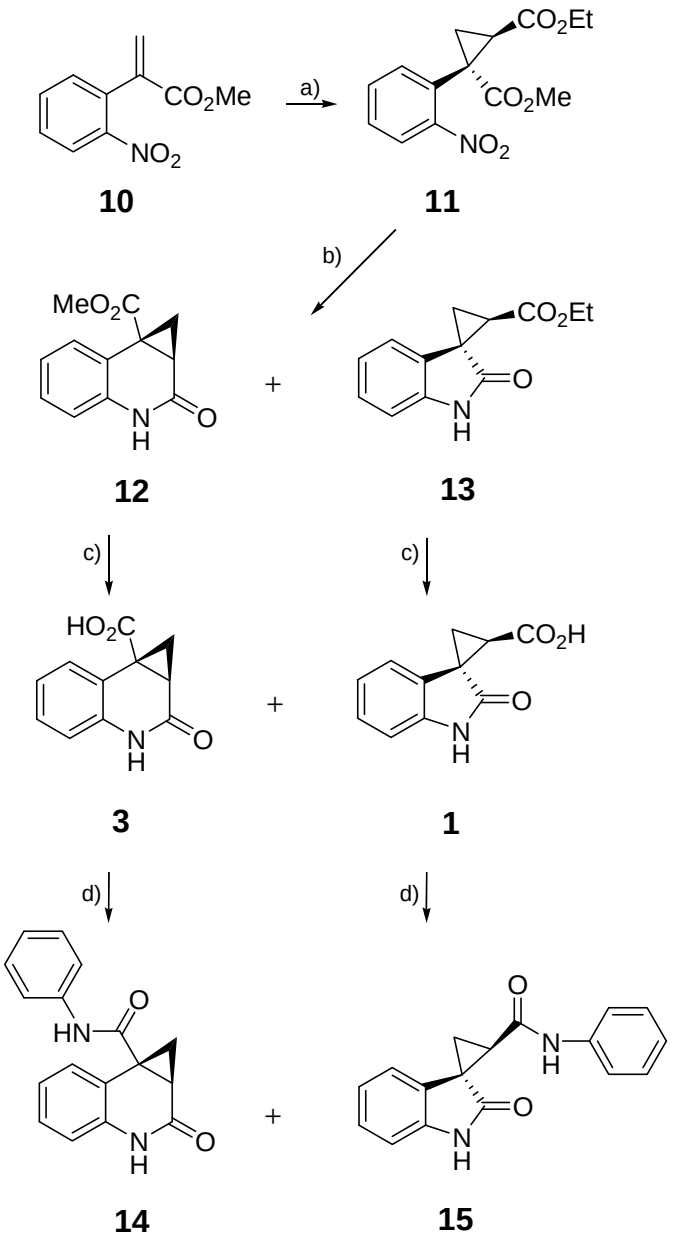


Figure 1 Single-crystal X-ray crystallographic structure of **11**.

Scheme 1[a] (Compounds **1**, **2** and **11 - 15** are racemic)



[a] *Reagents and conditions*: (a) $Me_2S(+)CH_2CO_2Et$ (2 equiv), DBU (1.5 equiv), anhydrous toluene, 20 h, 80%; (b) Zn dust (40 equiv), EtOH, H_2O, HCl, reflux, 3 h (12 : 1 of **12** : **13**), 70% (**12**), 5% (**13**) or H_2, Pd/C, 2 d (4 : 1 of **12** : **13**), 61% (**12**), 18% (**13**); (c) K_2CO_3, (2 equiv), $MeOH/H_2O$, sealed tube, 60 °C, 18 h, 50% (**3**), 80% (**1**); (d) Aniline (1.6 equiv), HOBT (1 equiv), EDCI (1 equiv), anhydrous MeCN, RT, 3 d, 77% (**14**), 18% (**15**).

Reductive cyclization of **11** using zinc and HCl under refluxing conditions, led to the formation of the expected products, **12** and **13**. This reaction was highly regioselective (**12** : **13** = 12 : 1) in favour of the formation of the quinoline **12** over the indolone **13**. In contrast, catalytic hydrogenation of **11** using Pd/C and H_2 led to a less regioselective reaction providing a 4 : 1

mixture of **12** and **13**, in favour of the quinoline product **12**. The higher regioselectivity found in the former method may be due to Zn^{2+} activation of the less hindered ester carbonyl by coordination, leading to more of the quinoline product **12**. Compounds **12** and **13** were readily separated by column chromatography and their structures were established by single-crystal X-ray crystallographic analysis (Figure 2). The ^{1}H NMR spectral data of **13** at 300 MHz was similar to that reported in 1978 by Bennet[5] for the same compound at 60 MHz. We thus we assume that the same diastereomeric compound was produced from these two different synthetic routes. Furthermore, the ^{1}H NMR spectral data for the cyclopropane resonances of **13** matched very closely to the analogous *N*-methyl analogue of **13** that was recently reported.[7] Saponification of **12** and **13** gave the carboxylic acids, **3** and **1**, respectively which were converted to their respective amide derivatives **14** and **15**, under EDCI/HOBT coupling conditions with aniline.

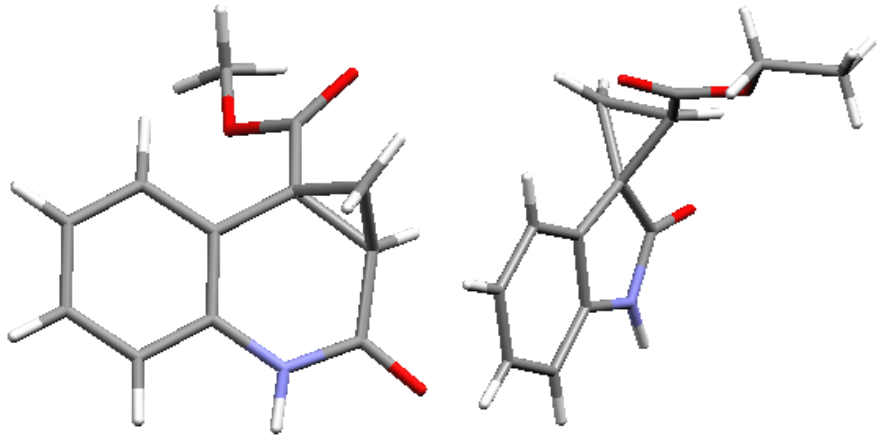
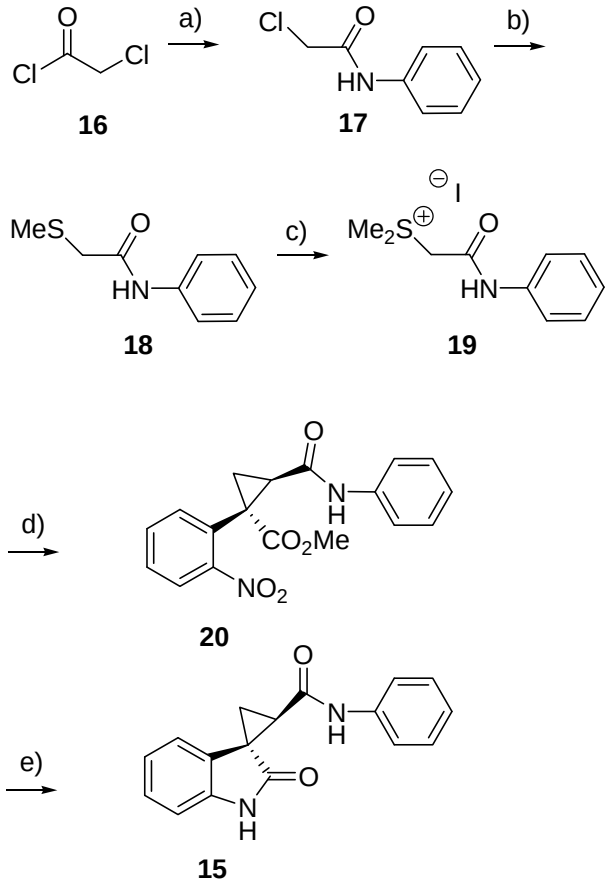


Figure 2 Single-crystal X-ray crystallographic structures of **12** (left) and **13** (right).

A more direct method to synthesise the indolone amide **15**, involved cyclopropanation of the acrylate **10** with the ylide derived from the sulfonium salt **19**, which was readily prepared in three synthetic steps from chloroacetyl chloride **16**, as outlined in Scheme 2. This ylide has been prepared previously from the reaction of dimthylsulfoxonium methylide and phenylisocyanate, however its subsequent reactions were not reported.[13] Although far less common than their ester-

sulfonium analogues, amide-sulfonium salts like **19** have been previously used for the cyclopropanation reactions of electron deficient alkenes, however normally as the secondary amide.[14]

Scheme 2[a] (Compounds **15** and **20** are racemic)



[a] *Reagents and conditions*: (a) Aniline (1.1 equiv), pyridine (1.5 equiv), anhydrous CH_2Cl_2, 0 °C→RT, 1 h, 74%; (b) MeSNa (1.1 equiv), anhydrous MeOH, RT, 15 min, 98%; (c) MeI (10 equiv), anhydrous CH_2Cl_2, RT, 2 d, 52%; (d) **10**, **19** (1.5 equiv), DBU (1.1 equiv), anhydrous CH_2Cl_2, RT, 2 d, 39% (b) Fe (8 equiv), AcOH, EtOH, sonication, 2 h, 60%.

The cyclopropanation reaction of the acrylate **10** and the ylide generated *in situ* from the sulfonium salt **19** (1.5 equiv) with DBU (1.1 equiv) in anhydrous DCM for 2 d at RT yielded solely the *trans* product **20** in an unoptimised yield of 39%. The structure of **20** was unequivocally established by single-crystal X-ray structural analysis (Figure 3). The reductive cyclisation of **79**, using the

methods described in Scheme 1, however were not productive. Previously it was found that cyclisation of indolones can proceed using iron with acetic acid under sonication.[10] This method successfully yielded the desired product **75** in a yield of 60%.

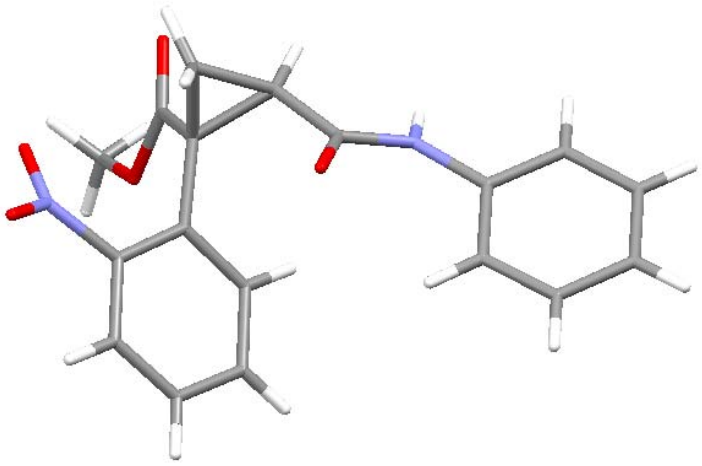


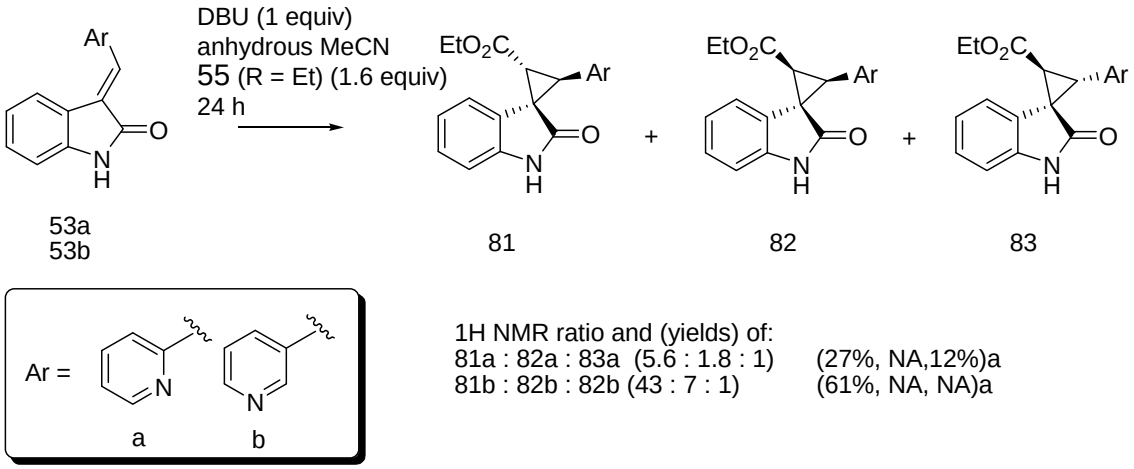
Figure 3 Single-crystal X-ray crystallographic structure of **20**.

For the preparation of target molecules **2**, the α-methylene indolinones **53a** and **53b** were prepared according to the literature.[11] Their *E*-geometries were unequivocally established by single-crystal X-ray structural analysis.[ref] The cyclopropanation of either **53a** or **53b** with EDSA in anhydrous acetonitrile for 24 h at RT yielded a mixture of three diastereomeric cycloprpanes products

Scheme 3.1). For the reaction using **53a**, ^{1}H NMR analysis of the crude reaction mixture revealed a 5.6 : 1.8 : 1 mixture of the diastereomeric products, **81a**, **82a** and **83a**, respectively. In contrast, the cyclopropanation reaction using **53b** proved to be a much more diastereoselective reaction giving a 43 : 7 : 1 mixture of the diastereomeric products, **81b**, **82b** and **83b**, respectively. Separation of these diastereomeric products by column chromatography proved difficult and only compounds **81a** and **83a** could be isolated diastereomerically pure in yields of 27% and 12% yields, respectively. The remaining chromatographic fractions consisted of mixtures of all three isomers. In contrast the

major *trans* isomer **81b**, was readily isolated in diastereomerically pure form in 61% yield from **53b**. Diastereomerically pure samples of the other isomers however, could not be obtained.

Scheme 3.1[a] (all compounds are racemic)



[a] Yields refer to diastereomerical pure compounds.

The structure of **81b** was unequivocally established by single-crystal X-ray structural analysis (**Figure 3.3**). The assignment of the relative stereochemistries of the diastereomeric products produced in Scheme 3 was based on the coupling constants observed for the cyclopropane methines, CH-3` and CH-2`. The chemical shifts and coupling constants for the major isomers of both reactions (**81a** and **81b**), and corresponding minor isomers according to prevalence ((**82a** and **82b**) and (**83a** and **83b**)) were almost identical, indicative of their same relative configurations. For the isomeric set, **81a**-**83a** the methine cyclopropane ^{1}H NMR resonances appeared as doublets for all diastereomers, with one methine of the major isomer **81a** having the most downfield signal (δ 3.93) and one at δ 3.46. For the isomer **83a** both cyclopropane methines had very similar chemical shifts and appeared almost like an ABq (δ 3.86 and 3.82). While one methine for the isomer **82a** had the most upfield signal (δ 3.08) and one at δ 3.57. The vicinal coupling constants for two of the

products, **81a** and **83a**, was found to be the same, ^{3}J ~ 8.1 Hz. This was in contrast to isomer **82a**, which had a vicinal coupling constant of ^{3}J ~ 10 Hz. Since in cyclopropanes, *cis*-vicinal coupling constants (^{3}J *cis* (H_bH_c) 6-12 Hz) are usually larger than *trans*-vicinal coupling constants (^{3}J *trans* (H_aH_c) 4-8 Hz)[12] the major diastereomer, **81a** and **81c** were assigned the 1,2-trans stereochemistries while the second most prominent isomer (**82a**) was the *cis* isomer.

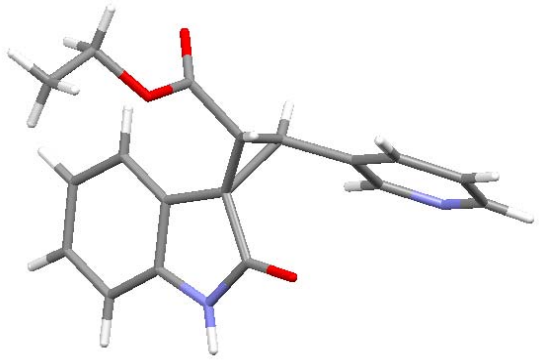
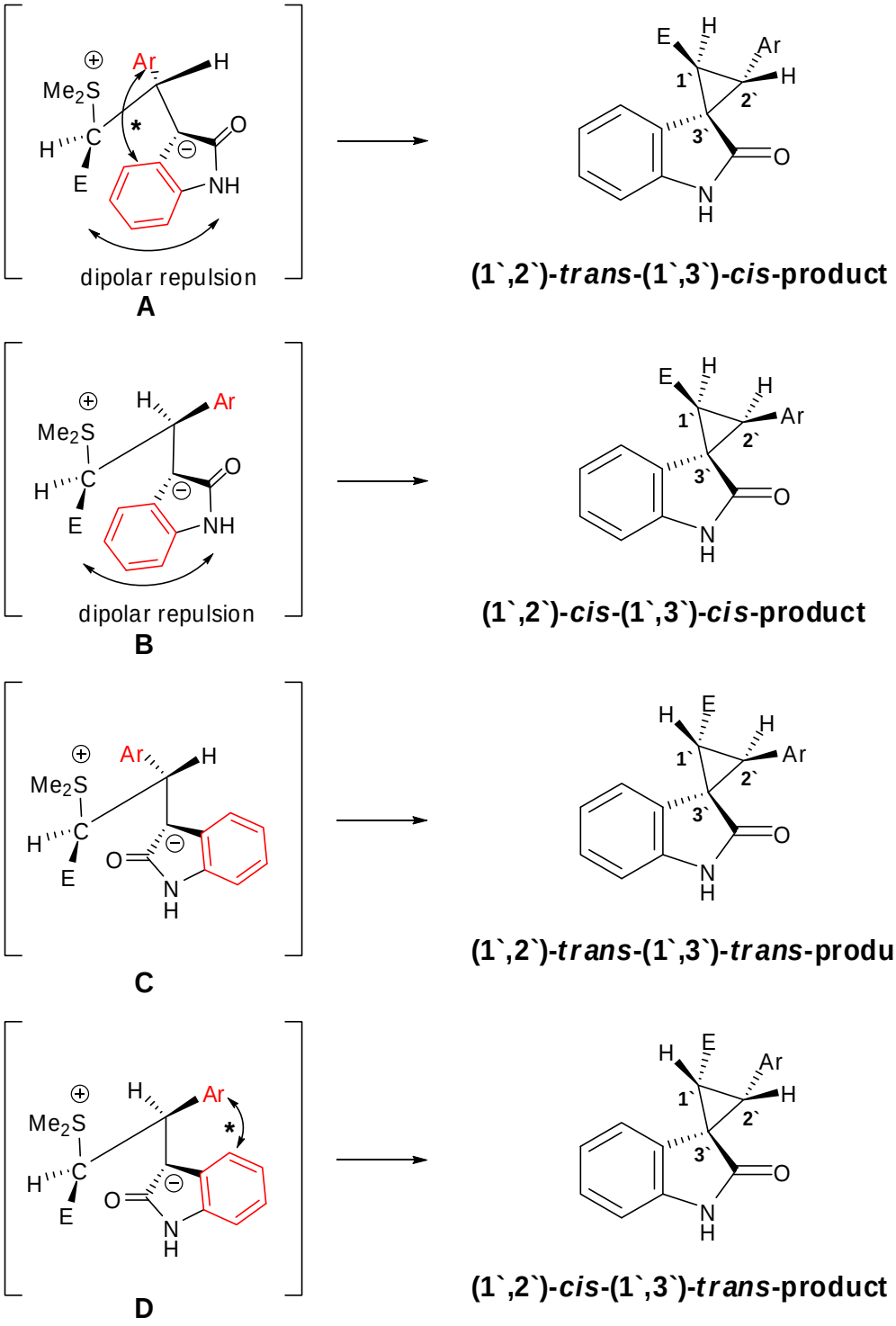


Figure 3.3 Single-crystal X-ray crystallographic analysis of **81a** (left) and **81b** (right).

Of the four possible racemic *anti* betaine intermediates involved in these reactions, the



* Unfavourable steric interaction between aromatic groups

E = electron-withdrawing group COPh or CO_2Et

In conclusion, the cyclopropanation reaction utilising sulfur ester and amide ylides has proven to be a good method of synthesising spirocyclopropane-1`,3-indoles. Compounds **53a**, **53b**, **81a**, **81b** and **83a** were submitted for cytostaticity studies and protein inhibition studies and the results of these are discussed in Chapter 6.

[a] *Reagents and conditions*: (a)

[a] *Reagents and conditions*: (a) K_2CO_3 (2 equiv), MeOH/H_2O, high pressure tube, 60°C, 5 h, 94%; (b) Aniline or 4-*N*,*N*-dimethylaminoaniline (1.7 equiv), HOBT (1 equiv), EDCI (1 equiv), MeCN, 0°C→RT, 15 h, 92% (**33a**), 44% (**33b**).

3. Cytotoxicity Studies

Compounds **15**, **25a**,**b**, **27**, **31**, **33a,b**, **41**, **42**, **43** and **44** were all tested for their cytotoxic activity against the cancer cell lines H460 (human non small cell lung), MCF-7 (human breast) and SF-268 (human CNS) at the Peter MacCallum Cancer Centre, St Andrew's Place, East Melbourne, Vic, 3002, Australia. Biological testing was performed using standard NCI procedures at a drug concentration of 25 μM (5 mM drug stocks were prepared in DMSO. Cells were then exposed to 25 μM of each drug for 72 h. The cells were then fixed, stained with SRB and the percentage cell

growth relative to the solvent control determined). Percent cell growth calculated from this testing showed little or no cytotoxic activity. The best activity was 50% cell growth at 25 μM for **33b** against H460.

In conclusion, we have developed a new strategy for the synthesis of both racemic and enantio-enriched versions of the 2-azaspiro[4.4]nonan-1-one and spiro[cyclopentane-1,1'-[1H]isoindol]-3'(2'H)-one ring systems using the phosphine-catalysed [3+2]-cycloaddition of both ester (**7a**) and amide derivatives (**7c**) of 2-butynoic acid. Enantiomerically enriched versions of **2** can be obtained using a chiral (1*S*)-camphor sultam derivative **7b** of 2-butynoic acid. We have also demonstrated the potential of these compounds as scaffolds for developing libraries of novel spiro-heterocyclic compounds.

4. Experimental

For X-ray structure determinations see supporting information. All ^{1}H NMR spectra were performed at 300 MHz and all ^{13}C NMR (DEPT) spectra at 75 MHz in $CDCl_3$ solution, unless otherwise noted. **Abbreviations**: PS (petroleum spirit, bp 40-60°C) and DCM (dichloromethane).

5. References

1. Williams, R. M.; Cox, R. J. *Accts. Chem. Res.* **2003**, *36*, 127-139. Lopez-Gresa, M. Pilar; Gonzalez, M. Carmen; Ciavatta, Letizia; Ayala, Ildefonso; Moya, Pilar; Primo, Jaime. J. Agric. Food Chem. **2006**, *54*, 2921-2925. Mugishima, T.; Tsuda, Masashi; K., Yuu; I., Haruaki; Fukushi, E.; Kawabata, J.; Watanabe, M.; Akao, K.; Kobayashi, J. *J. Org. Chem.* **2005**, *70*, 9430-9435.

2. (a) Jiang, T.; Kuhen, K. L.; Wolff, K.; Yin, H.; Bieza, K.; Caldwell, J.; Bursulaya, B.; Wu, T. Y.-H.; He, Y. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2105-2108. (b) Ding, K.; Lu, Y.; Nikolovska-Coleska, Z.; Wang, G.; Qiu, S.; Shangary, S.; Gao, W.; Qin, D.; Stuckey, J.; Krajewski, K.; Roller, P. P.; Wang, S. J. Med. Chem. **2006**, *49*, 3432-3435. (c) Rajeswaran, W. G.; Labroo, R. B.; Cohen, L. A. *J. Org. Chem.* **1999**, *64*, 1369-1371. (d) Robertson, D. W.; Krushinski, J. H.; Pollock, G. D.; Wilson, H.; Kauffman, R. F.; Hayes, J. S. *J. Med. Chem.* **1987**, *30*, 824-829.

3. For some recent synthetic studies see: Alcaide, B.; Almendros, P.; Rodriguez-Acebes, R. *J. Org. Chem.* **2006**, *71*, 2346-2351. Poornachandran, M.; Muruganantham, R.; Raghunathan, R. *Synth. Commun.* **2006**, *36*, 141-150. Nair, V.; Vellalath, S.; Poonoth, M.; Mohan, R.; Suresh, E. *Org. Lett.* **2006**, *8*, 507-509. Alcaide, B.; Almendros, P.; Rodriguez-Acebes, R. *Chem. Eur. J.* **2005**, 11, 5708-5712.

4.Yong, S. R.; Williams, M. C.; Pyne, S. G.; Ung, A. T.; Skelton, B. W.; White, A. H.; Turner, P. *Tetrahedron* **2005**, *61*, 8120-8129.

5. Mason, R. B.; Shapiro, M. J. *J. Org. Chem.* **1978**, *43*, 4383-4385.

6. Franke, A. *Liebigs Annal. Chemie* **1978**, 5, 717-725.

7. Shanmugam, P.; Vaithiyanathan, V.; Viswambharan, B. *Tetrahedron*, **2006**, *62*, 4342-4348.

8. Chiericato, M.; Croce, P. D.; Licandro, E. *J. Chem. Soc., Perkin I*, **1979**, 211-213.

9. Ellis, D.; Kuhen, K. L.; Anaclerio, B.; Wu, B.; Wolff, K.; Yin, H.; Bursulaya, B.; Caldwell, J.; Karanewsky D.; He, Y. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4246-4251.

10. Walker, G. N. *J. Am. Chem. Soc.* **1956**, *78*, 3698-3701. Selvakumar, N.; Reddy, B. Y.; Kumar, G. S.; Iqbal, J. *Tetrahedron Lett.* **2001**, *42*, 8395-8398. Hinman, R. L.; Bauman, C. P. *J. Org. Chem.* **1964**, *29*, 2431-2437.

11. Selvakumar, N.; Azhagan, A. M.; Srinivas, D.; Krishna, G. G. *Tetrahedron Lett.* **2002**, *43*, 9175-9178.

12. (a) Payne, G. B. *J. Org. Chem.* **1967**, *32*, 3351-3355. (b) Curley Jr., R. W.; DeLuca, H. F. *J. Org. Chem.* **1984**, *49*, 1944-1946.

13. Kaiser, C.; Trost, B. M.; Beeson, J.; Weinstock, J. *J. Org. Chem.* **1965**, *30*, 3972-3975. Konig, H.; Metzger, H. *Tetrahedron Lett.* **1964**, 3003-3005.

14. See for example: McAllister, G. D.; Oswald, M. F.; Paxton, R. J.; Raw, S. A.; Taylor, R. J. *Tetrahedron*, **2006**, *62*, 6681-6694. Ma, D.; Jiang, Y. *Tetrahedron: Asymmetry* **2000**, *11*, 3727-3736. Heras-Lopez A. M.; Pino-Gonzalez, M. S.; Sarabia-Garcia, F.; Lopez-Herrera, F. J. *J. Org. Chem.* **1998**, *63*, 9630-9634.

15. Gamble, A. B.; Keller, P. A. unpublished work, University of Wollongong, 2006.

16. Walker, G. N.; Smith, R. T.; Weaver, B. N., *J. Med. Chem.* **1965,** *8*, 626-637.

Acknowledgements

We thank the University of Wollongong for financial support and the Australian Research Council for a PhD scholarship to S.R.Y.