

SHORT STEP SYNTHESSES OF INDOLO[2,3-*a*]CARBAZOLES CARRYING AN ALKYL, ALLYL, OR A GLYCOSYL GROUP AT THE 11-POSITION AND A NOVEL 6,7-DIHYDRO-13*H*-CYCLOPENTANO[*mn*]INDOLO[3,2-*c*]-ACRIDINE DERIVATIVE ¹

Masanori Somei,* Fumio Yamada, Jun Kato, Yoshiaki Suzuki, and Yoshinori Ueda

Faculty of Pharmaceutical Sciences, Kanazawa University,
13-1 Takara-machi, Kanazawa 920-0934, Japan

Abstract — Novel 1-alkyl-, 1-allyl-, and 1- β -glycosyl-2,2'-biindolyis are prepared. Their Diels-Alder reaction produced 11-alkyl-, 11-allyl-, and 11- β -glycosylindolo[2,3-*a*]carbazoles. Formation of a novel 6,7-dihydro-13*H*-cyclopentano[*mn*]indolo[3,2-*c*]acridine derivative is also reported.

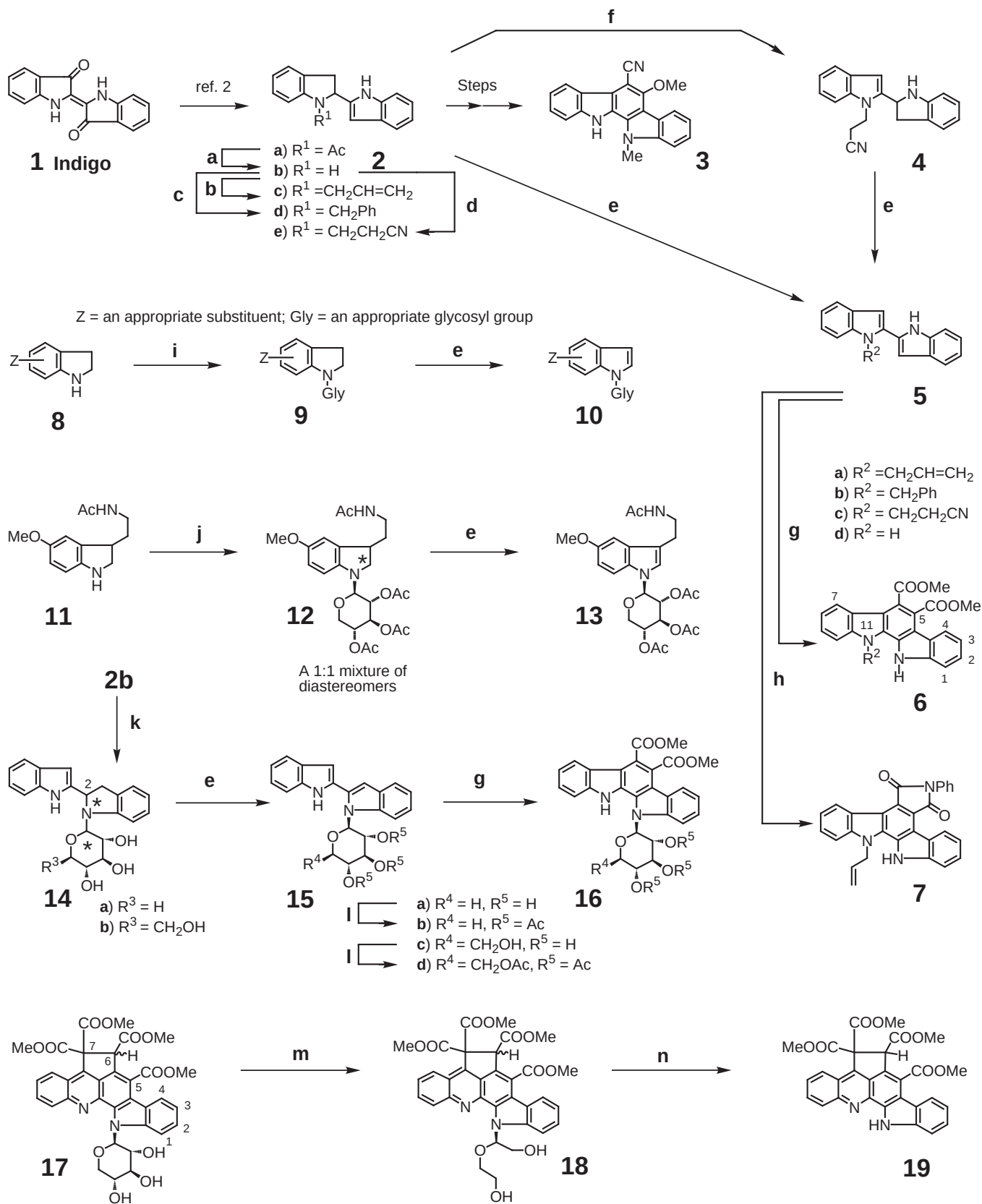
In our ongoing project to develop biologically active compounds, we have created a novel reaction for reducing indigo (**1**) to 1-acetyl-2,3-dihydro-2,2'-biindolyl² (**2a**) in 82% yield and demonstrated its versatility as a building block for producing 6-cyano-5-methoxy-12-methylindolo[2,3-*a*]carbazole derivatives³ (**3**) through 2,3-dihydro-2,2'-biindolyl⁴ (**2b**) (Scheme 1). In this communication, we wish to report a short step Diels-Alder approach⁵ to indolo[2,3-*a*]carbazoles carrying an alkyl, allyl or a glycosyl group at the 11-position utilizing **2b** as a synthetic intermediate. A novel formation of **17** upon treatment of the adducts, obtained by the reaction of 1-(β -D-xylopyranosyl)-2,2'-biindolyl (**15a**) with dimethyl acetylenedicarboxylate, with refluxing nitrobenzene is described as well.

N-Allylation of **2b** with allyl bromide in the presence of K₂CO₃ afforded **2c** in 90% yield. Subsequent DDQ oxidation in dioxane at room temperature provided 1-allyl-2,2'-biindolyl (**5a**) in 81% yield. Diels-Alder reaction of **5a** either with dimethyl acetylenedicarboxylate or *N*-phenylmaleimide in refluxing nitrobenzene produced **6a** and **7** in 46 and 52% yields, respectively.

The reaction of **2b** with benzyl bromide and K₂CO₃ proceeded in a quantitative yield to give **2d**. After converting **2d** to **5b** in 77% yield by DDQ oxidation, its Diels-Alder reaction with dimethyl acetylenedicarboxylate provided 64% yield of **6b**. Michael addition of **2b** to acrylonitrile gave a complex mixture of products. For this reason, the desired **2e** was obtained at best in only 19% yield under the examined conditions (NaH, KO^{*t*}Bu, or K₂CO₃ in DMF). An alternative trial using 3-bromopropionitrile in the presence of K₂CO₃ provided 56% yield of **4** as major product together with 4% yield of **2e**. DDQ oxidation of **2e** and **4** produced the same product (**5c**) in 69 and 63% yields, respectively. Subsequent Diels-Alder reaction of **5c** with dimethyl acetylenedicarboxylate provided 45% yield of **6c**.

The yields of **6** and **7** are greatly improved comparing with those (below 30% yield) obtained upon reactions of *N*-unsubstituted 2,2'-biindolyl (**5d**).^{5a} These results suggest that an introduction of an appropriate substituent onto the nitrogen atom of 2,2'-biindolyl is a good choice for improving the yield.

Scheme 1



a) NaOMe, MeOH, reflux; **b)** CH₂=CHCH₂Br, K₂CO₃, DMF, rt; **c)** PhCH₂Br, K₂CO₃, DMF, rt; **d)** CH₂=CHCN, NaH, DMF, 0°C; **e)** DDQ; **f)** BrCH₂CH₂CN, DMF, K₂CO₃, 98°C; **g)** dimethyl acetylenedicarboxylate, nitrobenzene, reflux; **h)** *N*-phenylmaleimide, nitrobenzene, reflux; **i)** an appropriate sugar; **j)** i) D-xylene, MeOH, reflux; ii) Ac₂O, pyridine, rt; **k)** D-xylene or D-glucose, MeOH, reflux; **l)** Ac₂O, pyridine, rt; **m)** i) NaIO₄, MeOH, H₂O, rt; ii) NaBH₄, MeOH, rt; **n)** 0.5N HCl, MeOH, reflux.

We next turned our attention to 11- β -glycosylindolo[2,3-*a*]carbazoles. So, we needed *N*-glycosylated indoles. Preobrazhenskaya and co-workers⁶ had reported a suitable glycosylation method to produce **10** without using any protecting group, consisting of heating indolines (**8**) with an appropriate sugar component, followed by DDQ oxidation of the resulting **9**. Combination of their method with the above Diels-Alder approach seemed to be promising to meet our end. We therefore first examined glycosylation method for the synthesis of 1-(β -D-xylopyranosyl)melatonin (**13**). Simple treatment of 2,3-dihydromelatonin⁷ (**11**) with D-xylose (3 mol eq) in refluxing MeOH, followed by acetylation with Ac₂O-pyridine, afforded a 1:1 mixture of diastereomers (**12**) in 85% yield. The mixture was oxidized to **13** in 56% yield with DDQ in dioxane at room temperature.

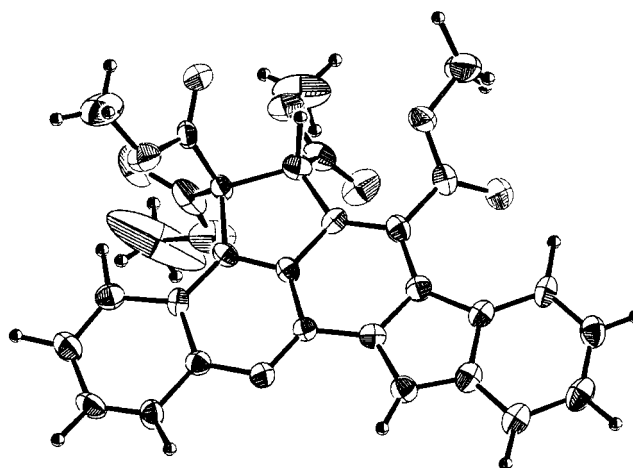
With this successful results, we allowed **2b** to react with D-xylose and D-glucose in refluxing MeOH. The reactions proceeded successfully resulting in the formations of the desired glycosylated products (**14a**) and (**14b**) in 98 and 86% yields, respectively. Although both **14a** and **14b** were inseparable mixtures of diastereoisomers, their oxidation with DDQ in dioxane at room temperature provided **15a** and **15c** as a single stereoisomer in 77 and 69% yields, respectively. These results clearly show that each of **14a** and **14b** is a mixture of stereoisomers at the 2-position. To determine the stereochemistry at the anomeric carbon, **15a** and **15c** were treated with Ac₂O-pyridine to give **15b** and **15d** in 93 and 82% yields, respectively. In the ¹H-NMR spectra of these compounds, anomeric protons are readily discernible and their coupling constants with the adjacent proton are found to be 10 Hz each, proving the presence of β -substituent. ¹H-NMR spectrum of **15c** exhibited that it exists as a 1:1 mixture of rotamers.⁸

Diels-Alder reaction of **15a** with dimethyl acetylenedicarboxylate in refluxing nitrobenzene was successful to provide the desired **16a** in 29% yield. Under similar reaction conditions, **15b** and **15c** produced **16b** and **16c** in 33 and 24% yields, respectively.

Introduction of a substituent into the nitrogen atom of 2,2'-biindolyl has improved the solubility to various solvents, even to Et₂O. This enabled us to apply Grieco's⁹ 5M LiClO₄ conditions to the reaction of **15a** with dimethyl acetylenedicarboxylate. As a result, **16a** was obtained in 30% yield together with nonpolar and polar adducts, each of them being a complex mixture of diastereomeric isomers. Heating of the former adducts in nitrobenzene at reflux for 1 h afforded **16a** in 35% yield. On the other hand, similar reaction of the latter adducts generated two novel products (**17a**) and (**17b**) in 8 and 8% yields, respectively.

Treatment of **17a** with methanolic HCl afforded a 1:1 mixture of **17a** and **17b**, proving that these compounds are stereoisomers at the stereogenic center (C-6) of the aglycon, which racemized easily. To

Figure 1
ORTEP DRAWING OF **19** (R = 0.087)



determine the structure of **17a**, deglycosylation was attempted with acids *in vain*. Therefore, **17a** was allowed to react with NaIO₄, followed by treatment with NaBH₄, to result in **18** as a single product in 83% yield. Acid hydrolysis of **18** proceeded easily to produce beautifully crystallized product (**19**) in 69% yield. The results of its X-Ray single crystallographic analysis are shown in Figure 1, which clearly shows that it has an unexpected 6,7-dihydro-13*H*-cyclopentano[*mn*]indolo[3,2-*c*]acridine skeleton. Studies are in progress on the mechanism of its formation and configurations at the C-6 positions of **17a** and **17b**.

In conclusion, we have succeeded in developing a simple synthetic methodology for producing various indolo[2,3-*a*]carbazoles from indigo. A synthetic route to a novel type of compounds having 6,7-dihydro-13*H*-cyclopentano[*mn*]indolo[3,2-*c*]acridine skeleton is discovered as well.

REFERENCES AND NOTES

1. a) Dedicated to the 70th birthday of Prof. J. P. Kutney. b) This is Part 108 of a series entitled "The Chemistry of Indoles". Part 107: M. Somei, S. Teranishi, K. Yamada, and F. Yamada, *Chem. Pharm. Bull.*, 2001, **49**, in press. All new compounds gave satisfactory spectral and elemental analysis or high-resolution MS data for crystals or oils, respectively. **2c**, 92.0—92.5 °C; **2d**, mp 148.5—150.5 °C; **2e**, mp 191—192 °C; **4**, oil; **5a**, mp 146.5—147.0 °C; **5b**, mp 173.5—176 °C; **5c**, mp 185—186 °C; **6a**, mp 194.5—196.5 °C; **6b**, mp 264.5—266.5 °C (decomp); **6c**, mp 277.5—278.5 °C (decomp); **7**, mp 247 °C (decomp); **13**, oil; **14a**, oil (mixture of diastereomers); **14b**, oil (mixture of diastereomers); **15a**, oil; **15b**, oil; **15c**, oil; **15d**, mp 176—179 °C; **16a**, viscous oil; **16b**, mp 283—285 °C; **16c**, mp 200.5—204.0 °C; **16d**, mp 225—228 °C; **17a** (polar), oil; **17b** (less polar), oil; **18**, oil; **19**, mp 143—144 °C.
2. M. Somei, H. Hayashi, and S. Ohmoto, *Heterocycles*, 1997, **44**, 169; M. Somei, H. Hayashi, T. Izumi, and S. Ohmoto, *ibid.*, 1995, **41**, 2161.
3. G. Knübel, L. K. Larsen, R. E. Moore, I. A. Levine, and G. M. L. Patterson, *J. Antibiot.*, 1990, **43**, 1236.
4. J. Kato, Y. Suzuki, H. Hayashi, and M. Somei, Abstract of Papers, 25th Symposium on Progress in Organic Reactions and Syntheses, Toyama, Japan, November, 1999, p. 240.
5. a) M. Somei and A. Kodama, *Heterocycles*, 1992, **34**, 1285. b) J. Bergman, "Studies in Natural Products Chemistry", Volume 1, ed. by Atta-ur-Rahman, Elsevier, 1988, pp. 3—30; T. Kaneko, H. Wong, K. T. Okamoto, and J. Clardy, *Tetrahedron Lett.*, 1985, **26**, 4015; J. Bergman and N. Eklund, *Tetrahedron*, 1980, **36**, 1439.
6. M. N. Preobrazhenskaya, *Usp. Khim.*, 1967, **36**, 1760 (*Chem. Abstr.*, 1968, **68**, 104846); M. N. Preobrazhenskaya and I. A. Korbukh, "Chemistry of Nucleosides and Nucleotides", Vol. 3, ed. by L. B. Townsend, Plenum Press, New York, 1994, pp.1—99 and references cited therein.
7. M. Somei, N. Oshikiri, M. Hasegawa, and F. Yamada, *Heterocycles*, 1999, **51**, 1237.
8. E. J. Gilbert, J. D. Chisholm, and D. L. V. Vranken, *J. Org. Chem.*, 1999, **64**, 5670.
9. P. A. Grieco, J. J. Nunes, and M. D. Gaul, *J. Am. Chem. Soc.*, 1990, **112**, 4595.