Pergamon

Tetrahedron Letters 42 (2001) 1049–1052

TETRAHEDRON LETTERS

7,7-Dimethyl-6,8-dioxabicyclo[3.3.0]oct-3-en-2-one as a synthetic equivalent of ketodicyclopentadiene: a new route to (−)-physostigmine, (−)-physovenine, and (−)-aphanorphine

Keigo Tanaka, Takahiko Taniguchi and Kunio Ogasawara*

Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980-8578, Japan

Received 24 November 2000; accepted 27 November 2000

Abstract—A new diastereocontrolled route to three alkaloids having a quaternary benzylic stereogenic center, (−)-physostigmine, (−)-physovenine, and (−)-aphanorphine, has been developed using enantiopure 7,7-dimethyl-6,8-dioxabicyclo[3.3.0]oct-3-en-2-one as a synthetic equivalent of chiral cyclopentadienone.

Quite recently, we developed an efficient preparation of enantiopure 7,7-dimethyl-6,8-dioxabicyclo[3.3.0]oct-3-en-2-one **1** in both enantiomeric forms from cyclopentadiene by employing lipase-mediated resolution in the key step.[1] Since this compound possesses a biased framework due to the protecting group of the dihydroxy functionality adjacent to the enone functionality, we are interested in utilizing it as a synthetic equivalent of chiral cyclopentadienone similar to ketodicyclopentadiene[2–4] **2**, in which its cyclopentene moiety plays dual roles as a protecting group of an olefin functionality and as a stereocontrolling device. We also take compound **1** as a synthetic equivalent of chiral cyclopentadienone, one of whose olefin functionalities being blocked by the 1,3-dioxolane ring at the same time brings about the molecular bias, just as the cyclopentene moiety of **2** does. We could, therefore, utilize the former **1**, which is more readily accessible, as a substitute for the latter, provided that its 1,3-dioxolane moiety could serve as the cyclopentene moiety in **2** (Fig. 1).

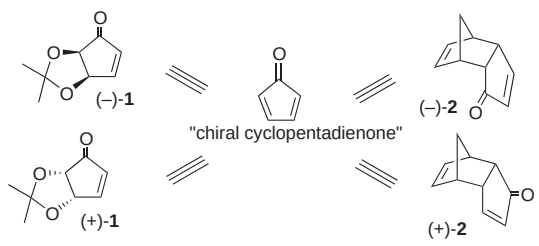


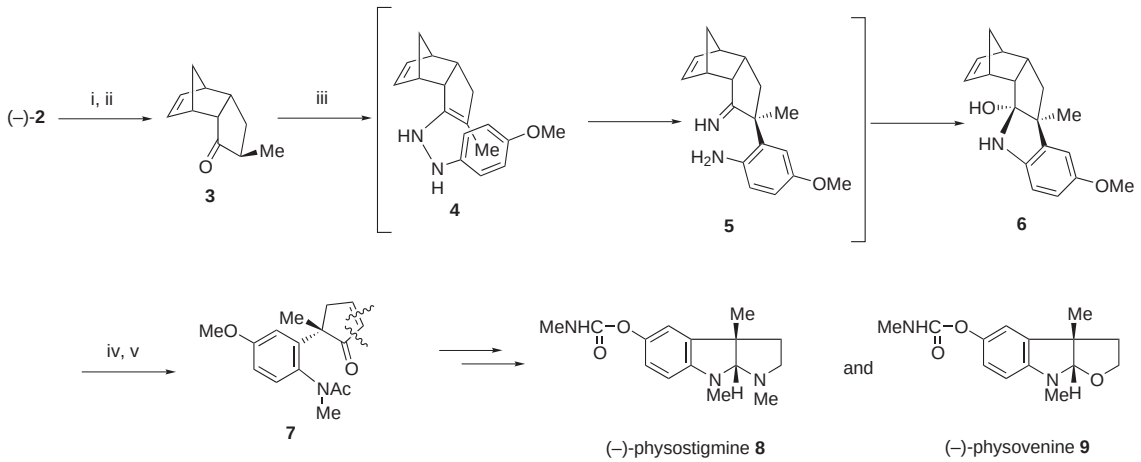
Figure 1.

In this letter, we report an alternative route to the Calabar bean alkaloids,[6] (−)-physostigmine **8** and (−)-physovenine **9**, and the norbenzomorphan natural alkaloid, (−)-aphanorphine[7] **25**, from the former with its 1,3-dioxolane ring serving as the cyclopentene moiety of the latter on the basis of the methodology[8] developed for the latter. As shown in our previous synthesis,[8] the stereochemistry of the target molecules was controlled by the molecular bias exerted by the cyclopentene moiety of the intermediate **3**, obtained from the latter by sequential 1,4-reduction and alkylation, under Fischer indolization conditions. The Fischer indolization reaction occurred diastereoselectively from the less hindered convex-face to give the carbinolamine **6**, presumably via **4** and **5**. The aminal moiety of the target molecules is then constructed after regeneration of the olefin functionality by retro-Diels–Alder removal of the cyclopentene moiety (Scheme 1). The same strategy may be applicable to the former enone **1** if it could afford the α-methyl-ketone **12**, and the resulting ketone **12** carrying the acid-sensitive 1,3-dioxolane ring could be tolerable under Fischer indolization conditions.

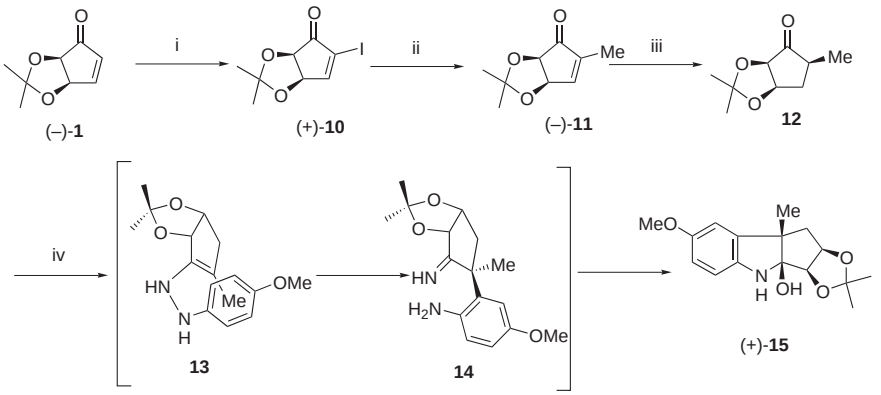
In order to demonstrate the utilization of the former enone **1** as a substitute for the latter enone **2** in the synthesis of the Calabar bean alkaloids, (−)-**1** was first transformed into the α-methyl-enone (−)-**11**, mp 48°C, $[\alpha]_D^{28}$ −17.7 (*c* 0.9, $CHCl_3$), via the α-iodo-enone (+)-**10**, mp 84°C, $[\alpha]_D^{29}$ +12.2 (*c* 0.9, $CHCl_3$), by employing the established procedure[5] involving the α-iodination[9] and the palladium-mediated cross-coupling reactions.[10] Catalytic hydrogenation of (+)-**11** yielded the α-methyl-ketone **12** as a mixture of two epimers. Thus, introduction of the α-methyl functionality could be

* Corresponding author. E-mail: konol@mail.cc.tohoku.ac.jp

0040-4039/01/$ - see front matter
PII: S0040-4039(00)02171-7



Scheme 1. Reagents and conditions: (i) Zn, AcOH. (ii) LDA, MeI, THF. (iii) 4-Methoxyphenylhydrazine hydrochloride, aqueous pyridine (1:10), reflux. (iv) Ac_2O, pyridine. (v) NaH, MeI, THF–DMF (1:1).

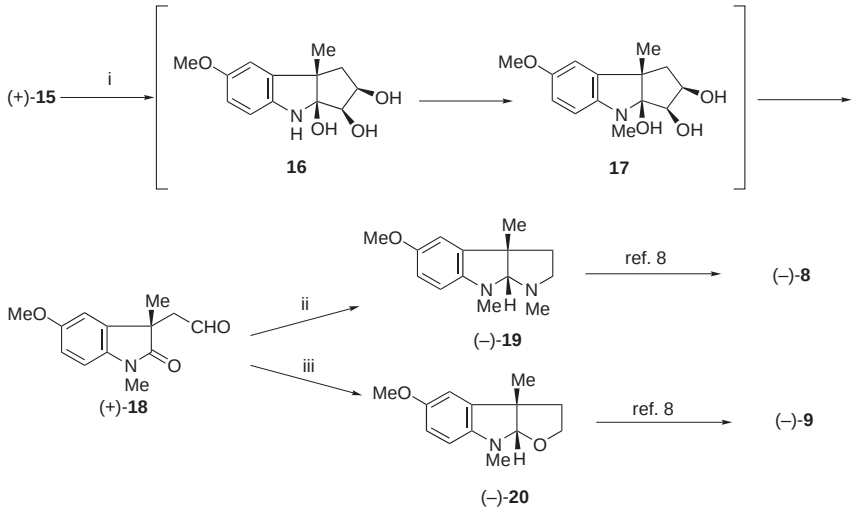


Scheme 2. Reagents and conditions: (i), I_2, pyridine–CCl_4, rt (83%). (ii) Me_4Sn, $PdCl_2(PhCN)_2$, CuI, Ph_3As, *N*-Me-pyrrolidone, 75°C (76%). (iii) H_2, 10% Pd–C, MeOH. (iv) 4-Methoxyphenylhydrazine hydrochloride, aqueous pyridine (1:10), reflux (71% from (+)-**11**).

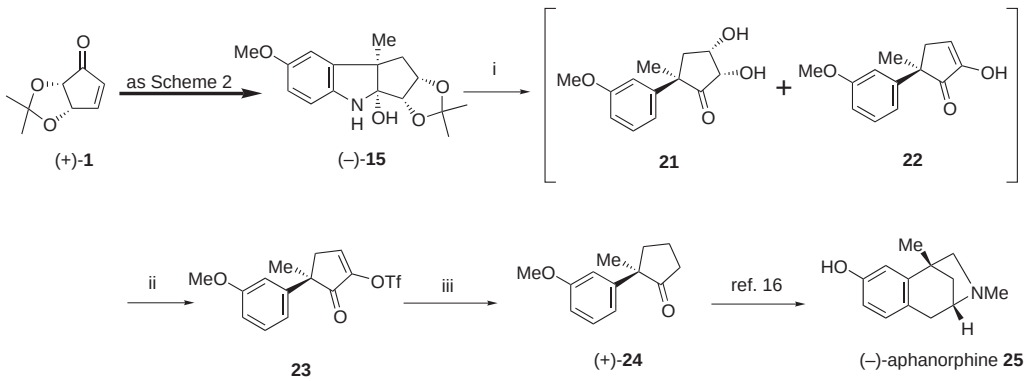
accomplished, keeping the 1,3-dioxolane moiety intact, without employing strong basic conditions. On reflux with 4-methoxyphenylhydrazine hydrochloride in aqueous pyridine,[8,11] **12** furnished the carbinolamine (+)-**15**, mp 130–132°C, $[\alpha]_D^{23}$ +6.5 (*c* 1.0, $CHCl_3$), in satisfactory yield as a single product without affecting the dioxolane moiety. It is noteworthy that the dioxolane moiety controlling the diastereoselectivity was stable under the Fischer indolization conditions employed. Overall yield of (+)-**15** from (–)-**1** was 45% in four steps (Scheme 2).

Having served its dual purpose as a stereocontrolling device and protecting group, the 1,3-dioxolane group of (+)-**15** was next hydrolysed. Thus, (+)-**15** was treated with hydrochloric acid to give the triol **16**, which was immediately treated with 37% formalin and sodium triacetoxyborohydride, followed by sodium periodate in aqueous sodium hydrogen carbonate solution to furnish *N*-methyloxyindole **18**, mp 116–118°C, $[\alpha]_D^{24}$ +15.7 (*c* 1.0, $CHCl_3$), in 52% overall yield via the transient *N*-methyltriol **17** with loss of one carbon moiety. Thus, the dioxolane moiety of **1** played the same role as the cyclopentene moiety of **2**, the removal of which required high temperature. On reduction with lithium aluminum hydride in THF, **18** afforded the known tricyclic aminoacetal[8,13] (–)-**20**, mp 33°C, $[\alpha]_D^{23}$ –94.4 (*c* 0.7, $CHCl_3$) [lit.[8]: $[\alpha]_D^{32}$ –96.2 (*c* 0.35, $CHCl_3$)], the key intermediate of (–)-physovenine[12] **9**, directly in 67% yield by reductive cyclization. On the other hand, **18**, on condensation with methylamine followed by reduction of the resulting imine with lithium aluminum hydride afforded (–)-**19**, $[\alpha]_D^{23}$ –139.0 (*c* 0.7, benzene) [lit.[8]: $[\alpha]_D^{34}$ –134 (*c* 0.7, benzene)], known as esermethole[6] and the key intermediate of (–)-physostigmine[12] **8**, in 54% overall yield, by sequential reductive amination and reductive cyclization. Thus, an alternative route to two Calabar bean alkaloids has been developed using 7,7-dimethyl-6,8-dioxabicyclo[3.3.0]-oct-3-en-2-one (–)-**1** as the substitute for the previously used ketodicyclopentadiene (–)-**2** employing the same methodology (Scheme 3).

Enantiomeric (+)-7,7-dimethyl-6,8-dioxabicyclo[3.3.0]-oct-3-ene (+)-**1** could also be used for an alternative



Scheme 3. Reagents and conditions: (i), 2N HCl–THF (1:3), 37% formalin, $NaBH(OAc)_3$, then $NaIO_4$, $NaHCO_3$ (52%). (ii) Methylamine hydrochloride, Et_3N, $MgSO_4$, CH_2Cl_2, rt, then $LiAlH_4$, THF, reflux (54%). (iii) $LiAlH_4$, THF, 0°C (67%).



Scheme 4. Reagents and conditions: (i) $NaNO_2$, H_3PO_2, H_2O, rt. (ii) $PhNTf_2$, Et_3N, DMAP (cat.), CH_2Cl_2, rt. (iii) H_2, 10% Pd–C, *i*-Pr_2NEt, MeOH, rt (56% from (–)-**15**).

synthesis of (–)-aphanorphine **25**, the only known norbenzomorphan natural product isolated from the freshwater blue-green alga *Aphanizomenon flos-aquae*. Thus, employing the exact same procedure as for the enantiomeric counterpart, (+)-**1** was transformed into the enantiomeric carbinolamine (–)-**15**, mp 130–131°C, $[\alpha]_D^{23}$ −5.5 (*c* 0.9, $CHCl_3$), in a comparable overall yield. Upon exposure to sodium nitrite in aqueous hypophosphorus acid,[13,14] (–)-**15** afforded a mixture of the dihydroxy-ketone **21** and the diosphenol **22** by concurrent diazotization and reductive removal of nitrogen with hydrolysis of the dioxolane functionality and β-dehydration to some extent under the conditions. The mixture without separation was triflated to give rise to the single enol triflate **23** with concurrent β-dehydration of the diol **21** under the conditions. Finally, catalytic hydrogenation of **23** in the presence of Hünig base[15] yielded the cyclopentanone (+)-**24**, $[\alpha]_D^{25}$ +93.7 (*c* 0.8, $CHCl_3$) [lit.[16]: $[\alpha]_D^{27}$ +83.2 (*c* 1.21, $CHCl_3$)], previously obtained from (–)-**1** and used for the key intermediate of the first synthesis[16] of (–)-aphanorphine **25**. The overall yield of (+)-**24** from the carbinolamine (–)-**15** was 56% in three steps (Scheme 4).

In summary, we have demonstrated that enantiopure 7,7-dimethyl-6,8-dioxabicyclo[3.3.0]oct-3-ene **1** could serve as the substitute for enantiopure ketodicyclopentadiene **2** in the enantio- and diastereo-controlled synthesis of (–)-physostigmine **8**, (–)-physovenine **9**, and (–)-aphanorphine **25**. In the present synthesis, the former exhibited the same chemical and steric characteristics as the latter as a synthetic equivalent of chiral cyclopentadienone.

References

1. Nakashima, H.; Sato, M.; Taniguchi, T.; Ogasawara, K. *Synthesis* **2000**, 817.
2. A pertinent review, see: Ogasawara, K. *J. Syn. Org. Chem. Jpn.* **1996**, *54*, 15.
3. Sugahara, T.; Kuroyanagi, Y.; Ogasawara, K. *Synthesis* **1996**, 1101.
4. Ogasawara, K. *Pure Appl. Chem.* **1994**, *66*, 2119.
5. We have already demonstrated their equivalent use in an enantiocontrolled synthesis of (+)-estrone in which the Diels–Alder reaction was used as the key reaction, see:

Tanaka, K.; Nakashima, H.; Taniguchi, T.; Ogasawara, K. *Org. Lett.* **2000**, *2*, 1915.
6. A pertinent review, see: Takano, S.; Ogasawara, K. In *The Alkaloids*, Brossi, A., Ed.; Academic Press: New York, 1989; Vol. 36, p. 225.
7. Gulavita, N.; Hori, A.; Shimizu, Y.; Laszlo, P.; Clardy, J. *Tetrahedron Lett.* **1988**, *29*, 4381.
8. Takano, S.; Moriya, M.; Ogasawara, K. *J. Org. Chem.* **1991**, *56*, 5982.
9. Johnson, C. R.; Adams, J. P.; Braun, M. P.; Senanayake, C. B. W. *Tetrahedron Lett.* **1992**, *33*, 917.
10. Bellina, F.; Carpita, A.; Ciucci, D.; DeSantis, M.; Rossi, R. *Tetrahedron* **1993**, *49*, 4677.
11. Welch, W. N. *Synthesis* **1977**, 645.
12. Recent enantiocontrolled synthesis, see: (–)-physostigmine—(a) Kawahara, M.; Nshida, A.; Nakagawa, M. *Org. Lett.* **2000**, *2*, 675. (b) ElAzab, A. S.; Taniguchi, T.; Ogasawara, K. *Org. Lett.* **2000**, *2*, 2757. (–)-Physovenine—(c) Matsuura, T.; Overman, L. E.; Poon, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 6500.
13. Sepiol, J. *Tetrahedron* **1986**, *42*, 609.
14. Takano, S.; Moriya, M.; Ogasawara, K. *Tetrahedron Lett.* **1992**, *33*, 329.
15. Kalwinsh, I.; Metten, K.-H.; Bruckner, R. *Heterocycles* **1995**, *40*, 939.
16. Takano, S.; Inomata, K.; Sato, T.; Takahashi, M.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1990**, 290.