

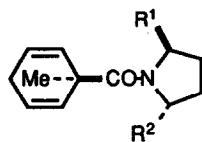
## Highly Enantioselective Creation of Quaternary Carbons in a Halolactonization of Bis- $\gamma,\delta$ -unsaturated Carboxylic Imides Derived from a Camphorsultam: Enantioselective Synthesis of (+)-Mesembrine

Tsutomu Yokomatsu, Haruo Iwasawa, and Shiroshi Shibuya\*

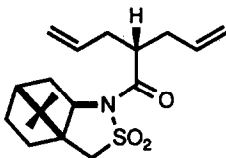
Tokyo College of Pharmacy, 1432-1 Horinouchi, Hachioji, Tokyo 192-03, Japan

**Abstract:** Iodolactonization of symmetrical diene-carboxylic imides (**3a,b**), derived from a camphorsultam, afforded chiral lactones (**5**) and (**6**) possessing aromatic substituents on quaternary carbons in high enantioselectivity with moderate diastereoselectivity.

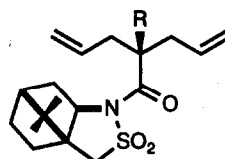
Creation of asymmetric quaternary carbon center is one of the most challenging problems in synthetic organic chemistry.<sup>1</sup> A number of methods have been reported recently for the highly enantioselective construction of quaternary carbon centers in various molecular frames.<sup>2</sup> Enantioselective halolactonization of symmetrical diene-carboxylic chiral amides (**1a,b**) having quaternary carbons through discrimination of diastereotopic alkene group with concomitant face differentiation was also pursued in order to obtain asymmetric synthons with diastereo- and enantioisomeric purity.<sup>3</sup> However it was rather difficult to achieve high enantioselectivity.<sup>3,4</sup> Recently we have found that iodolactonization of symmetrical diene-carboxylic imide (**2**) derived from a camphorsultam, proceeded in high degree of diastereo- and enantioselectivity.<sup>5</sup> In this paper, we report our finding on the iodolactonization of symmetrical diene-carboxylic imides (**3**) possessing aromatic substituents on quaternary carbons; this cyclization affords the chiral lactones in high yield as well as high enantioselectivity.



**1a:** R<sup>1</sup>=R<sup>2</sup>=Me  
**b:** R<sup>1</sup>=H, R<sup>2</sup>=CH<sub>2</sub>OH



**2**

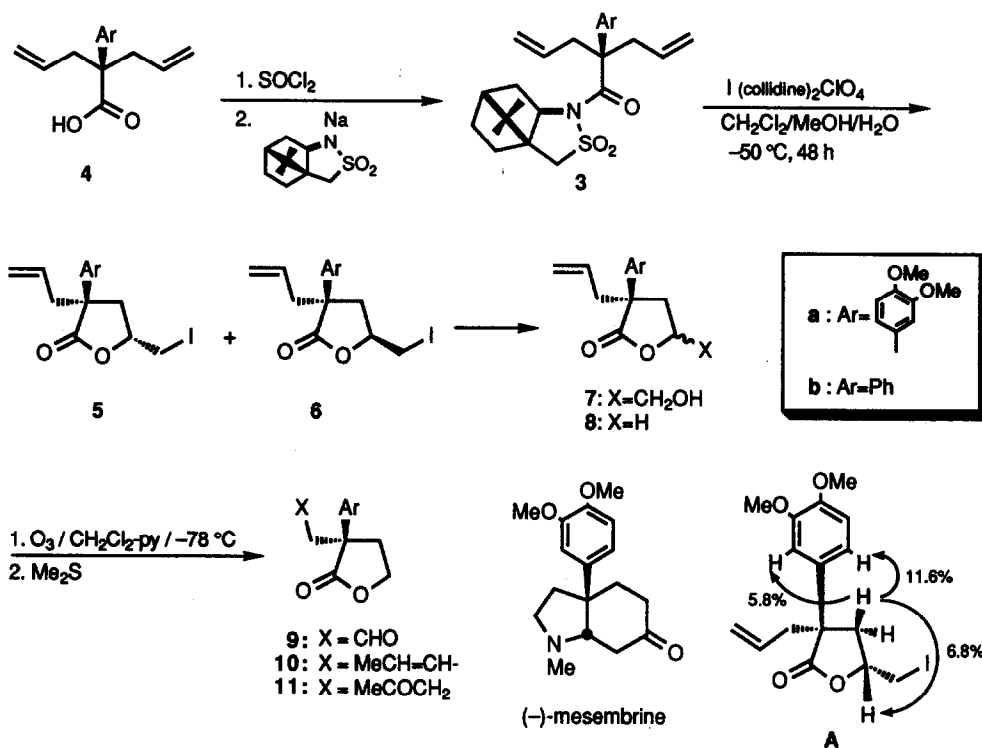


**3a:** R = 3,4-dimethoxyphenyl  
**b:** R = Phenyl  
**c:** R = Ethyl

Symmetrical diene-carboxylic acid (**4a**), prepared from ethyl 3,4-dimethoxyphenylacetate through sequential diallylation and saponification, was condensed with a sultam, derived from D-camphorsulfonic acid, under the methods<sup>6</sup> reported by Oppolzer, to give *N*-acylsultam (**3a**),<sup>7</sup> mp 151-153 °C [ $\alpha$ ]<sub>D</sub><sup>20</sup> -55.6° (c 1.1, CHCl<sub>3</sub>), in 65% yield. Treatment of **3a** with iodonium di-*syn*-collidine perchlorate (2.3 equiv.) in CH<sub>2</sub>Cl<sub>2</sub>-

MeOH containing 1.2 equiv. of H<sub>2</sub>O at -50 °C for 48 h gave a diastereoisomeric mixture of **5a**,<sup>8</sup> [ $\alpha$ ]<sub>D</sub><sup>20</sup>+43.0° (c 0.5, CHCl<sub>3</sub>), and **6a** in a ratio of 4.5 : 1 in 83% yield. The relative stereochemistry of **5a** and **6a** was established by NOE experiments on **5a**. Representative NOE data for **5a** are shown in A (Scheme 1). The enantiomeric excess (e.e.) of **5a** was determined to be 88% by <sup>1</sup>H NMR (300 MHz) analysis with (*S*)-(+)-9-anthryl trifluoromethylcarbinol as chiral solvating agent.<sup>9</sup>

Scheme 1

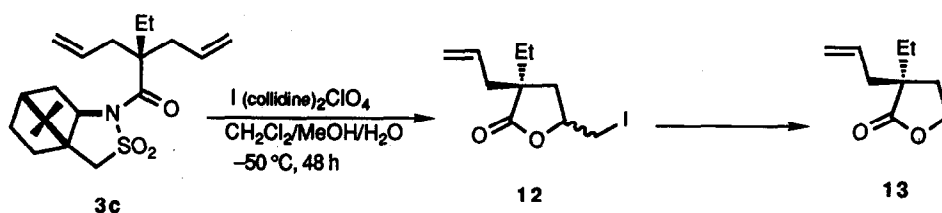


In order to ascertain absolute stereochemistry of the quaternary carbon centers in both diastereoisomers, deiodomethylations of **5a** and **6a** were carried out. Treatment of **5a** with aqueous potassium hydroxide (20%), followed by acid work-up (HCl) afforded  $\gamma$ -lactone (**7a**) quantitatively as a mixture of diastereoisomers. The compound (**7a**), on sequential saponification, periodate cleavage and reduction in MeOH in the same flask [1. 10% KOH then CO<sub>2</sub>, 2. NaIO<sub>4</sub>, 3. NaBH<sub>4</sub>], gave the lactone (**8a**),<sup>8</sup> [ $\alpha$ ]<sub>D</sub><sup>20</sup>+74.1° (c 0.5, MeOH), in 80% yield. Since **6a** could not be isolated as pure states, similar transformations as above were carried out on an 1.6 : 1 mixture of **5a** and **6a** to give **8a**. The sign of specific rotation and e.e. (88%)<sup>10</sup> of which were identical those from pure **5a**. Then, absolute stereochemistry on the quaternary carbons of **6a** was found to be same as that of **5a**. Thus for the synthesis of **8a**, a mixture of **5a** and **6a** was used, without separation, practically.

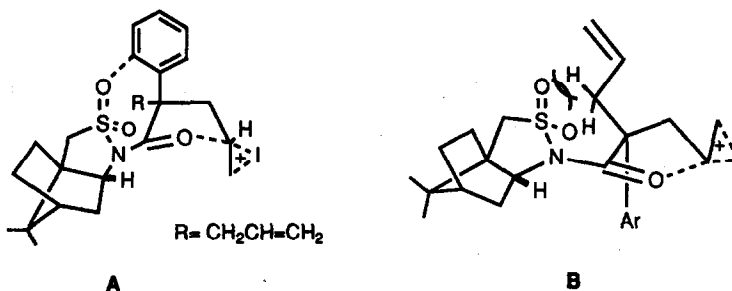
In the efforts to deduce absolute configuration, **8a** was converted to keto lactone **11a**. The absolute stereochemistry of (-)-**11a** has been already established by Takano and co-workers through chemical correlation

to natural (-)-mesembrine.<sup>11</sup> Ozonolysis of **8a** [1. O<sub>3</sub>, pyridine-CH<sub>2</sub>Cl<sub>2</sub>, -78 °C; 2. Me<sub>2</sub>S] gave aldehyde **9a**, [ $\alpha$ ]<sub>D</sub><sup>20</sup>+73.8° (c 1.04, CHCl<sub>3</sub>), as an oil in 70% yield. Wittig reaction of **9a** [MeCH=PPh<sub>3</sub>, THF], followed by palladium catalyzed oxidation<sup>12</sup> [PdCl<sub>2</sub>, CuCl, O<sub>2</sub>, wet DMF] gave the requisite methyl ketone **11a**, an oil, [ $\alpha$ ]<sub>D</sub><sup>20</sup>+69.1° (c 0.44, MeOH); lit.,<sup>11</sup> mp 78 °C, [ $\alpha$ ]<sub>D</sub><sup>20</sup>-42.6° (c 0.5, MeOH) for (-)-**11a**. Observed optical rotation of **11a** revealed that it was antipodal to that reported in the literature.<sup>11</sup> Thus, the stereochemistry of **5a** and **6a** was unambiguously assigned as shown in Scheme 1.

Iodolactonization of **3b**<sup>14</sup> under the same conditions as for **3a** proceeded similarly in a high enantioselectivity to give a diastereoisomeric mixture of **5b**, 84% ee,<sup>13</sup> [ $\alpha$ ]<sub>D</sub><sup>20</sup>+50.1° (c 1.05, CHCl<sub>3</sub>), and **6b** (**5b** : **6b** = 5.5 : 1, 65% yield). A mixture of **5b** and **6b** was converted to **8b**, [ $\alpha$ ]<sub>D</sub><sup>20</sup>+53.7° (c 0.3, MeOH), via **7b** through exactly the same procedure as for **8a**. It should be noted that aromatic substituents on quaternary carbons of **3** were quite important to induce the halolactonization with high enantioselectivity. Upon treatment of **3c**<sup>14</sup> possessing alkyl substituent such as ethyl with iodonium di-*sym*-collidine perchlorate under identical conditions to that used for **3a**, diastereoisomeric mixture (1 : 1) of **12**<sup>15</sup> was obtained in 75% yield. Optical purity of **13** derived from **12**, however, appeared to be very low (25%),<sup>4,16</sup> [**13**: [ $\alpha$ ]<sub>D</sub><sup>20</sup>-3.28° (c 0.36, MeOH), lit.,<sup>4</sup> [ $\alpha$ ]<sub>D</sub><sup>20</sup>+12.77° (c 3.1, MeOH) for (+)-**13**].



Although precise stereochemical course of the present iodolactonization is unclear at this stage, the results delineated in this paper strongly suggest that the observed enantioselection may not reflect on simple steric interaction alone.<sup>5</sup> Assuming two transition states A and B leading to **5a** and its enantiomer,<sup>17</sup> transition state A would be favored over B, because transition states A involves  $\pi$ -stacking stabilization between sulfone function and aromatic ring but in transition state B steric repulsion between sulfone oxygen and allyl substituent are presence. A clear understanding of the stereoselectivity in these halolactonization must await further experimentation.



In summary we have demonstrated a usefulness of iodolactonization of symmetrically diene-carboxylic imides possessing a sultam as chiral auxiliary to create quaternary carbon centers in high enantioselectivity. The results described in this paper also constitute enantioselective synthesis of (+)-mesembrine in a formal manner.<sup>11</sup>

#### REFERENCES AND NOTES

- For reviews: see a) Martin, S. F. *Tetrahedron* **1980**, *36*, 419. b) ApSimon, J. W.; Collier, T. L. *Ibid.* **1986**, *42*, 5157. c) *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1983.
- a) Takano, S.; Shimazaki, Y.; Moriya, M.; Ogasawara, K. *Chem. Lett.* **1990**, 1177. b) Isaka, M.; Nakamura, E. *J. Am. Chem. Soc.* **1990**, *112*, 7428. c) Lee, E.; Shi, I.-J.; Kim, T.-S. *J. Am. Chem. Soc.* **1990**, *112*, 260 and references cited therein.
- Hart, D. J.; Huang, H.-C.; Krishnamurthy, R.; Schwartz, T. *J. Am. Chem. Soc.* **1989**, *111*, 7507.
- Takano, S.; Murataka, C.; Imamura, Y.; Tamura, N.; Ogasawara, K. *Heterocycles* **1981**, *16*, 1291.
- Yokomatsu, T.; Iwasawa, H.; Shibuya, S. *J. Chem. Soc., Chem. Commun.*, **1992**, 728. Highly enantioselective halolactonization of symmetrical diene acids using (2*R*,5*R*)-bis(methoxymethyl)pyrrolidine as a chiral auxiliary was first reported by Fuji *et al.*; Fuji, K.; Node, M.; Naniwa, Y.; Kawabata, T. *Tetrahedron Lett.* **1990**, *31*, 3175.
- For review: Oppolzer, W. *Tetrahedron* **1987**, *43*, 1969.
- All new compounds gave satisfactory spectroscopic and analytical data.
- 5a**: an oil; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>, δ) 6.97 (1H, d, *J*=2.2 Hz), 6.91 (1H, dd, *J*=2.2, 8.5 Hz), 6.84 (1H, d, *J*=8.5 Hz), 5.71-5.58 (1H, m), 5.17-5.08 (2H, m), 4.30 (1H, dddd, *J*=4.8, 5.1, 7.5, 10.5 Hz), 3.90 (3H, s), 3.89 (3H, s), 3.43 (1H, dd, *J*=4.8, 10.3 Hz), 3.26 (1H, dd, *J*=7.5, 10.3 Hz), 2.88 (1H, dd, *J*=5.1, 13.2 Hz), 2.66 (2H, d, *J*=7.1 Hz), 2.12 (1H, dd, *J*=10.5, 13.2 Hz). **8a**: an oil; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>, δ) 7.05 (1H, d, *J*=2.3 Hz), 6.93 (1H, dd, *J*=2.3, 8.5 Hz), 6.83 (1H, d, *J*=8.5 Hz), 5.67-5.56 (1H, m), 5.14-5.06 (2H, m), 4.31 (1H, ddd, *J*=3.2, 8.9, 12.3 Hz), 4.12 (1H, ddd, *J*=6.4, 9.3, 12.3 Hz), 3.89 (3H, s), 3.87 (3H, s), 2.69-2.43 (4H, m).
- Pirkle, W. H.; Sikkenga, D. J. *J. Org. Chem.* **1977**, *42*, 1370.
- Determined by <sup>1</sup>H NMR (300 MHz) with Pirkle agent.<sup>9</sup>
- Takano, S.; Imamura, Y.; Ogasawara, K. *Tetrahedron Lett.* **1981**, *22*, 4479.
- Tsuji, J.; Shimizu, I.; Yamamoto, K. *Tetrahedron Lett.* **1976**, 2957.
- Determined by <sup>1</sup>H NMR (300 MHz) with Eu(hfc)<sub>3</sub>.
- 3b**: mp 141-142 °C, [α]<sub>D</sub><sup>20</sup>-47.9° (c 1.0, CHCl<sub>3</sub>). **3c**: mp 57-59 °C, [α]<sub>D</sub><sup>20</sup>+3.29° (c 1.0, CHCl<sub>3</sub>).
- Because it was difficult to separate individual stereoisomer of **12**, we could not determine the optical purities for each diastereoisomers; optical purity with one of diastereoisomers of the iodolactones, prepared by analogous iodolactonization of **3** (R=Me), could be directly determined as 25% e.e.<sup>13</sup>
- Absolute configuration and optical purity of **13** were determined by comparison of the optical rotation value with that in the literature.<sup>4</sup>
- In order to explain the observed diastereoselectivity (aromatic substituent *trans* to iodomethyl group), aromatic substituent is assumed to be as pseudoaxial configuration in the transition states.