Al-N distances are 1.952 (3) and 1.981 (3) Å for Al(1)-N(1) and Al(1)-N(2), respectively. The Al(1)-Cl(1) and Al(2)-Cl(1) bond distances of 2.509 (2) and 2.258 (2) Å, respectively, are longer than Al-Cl distances reported in two previously reported $AlCl_2$-crown ether complexes containing octahedral aluminum atoms: $[AlCl_2][12\text{-crown-4}]^+$ (2.202 (5) Å) and $[AlCl_2][18\text{-crown-6}]^+$ (2.148 (3) Å).[26] Indeed, the Al-Cl distances in the title compound are longer than the Al-Cl distances reported for the seven-coordinate aluminum atom in $[AlCl_2][benzo\text{-}15\text{-crown-5}]^+$ (2.202 (5) and 2.197 (7) Å).[27]

The isolation of the unusual organoaluminum compound has stimulated our interest in cyclam-zirconium systems. In future contributions we will continue to explore the role of transition-metal salts on the organoaluminum chemistry of macrocyclic amines.

Acknowledgment. We are grateful to the National Science Foundation for support of this work (Grant RII-8520554 to G.H.R.).

Supplementary Material Available: Tables of crystal data, bond distances and angles, final fractional coordinates, thermal parameters, and a summary of data collection and refinement and figures showing the atom labeling and cell packing (17 pages); a listing of observed and calculated structure factors (6 pages). Ordering information is given on any current masthead page.

(25) Barefield, E. K.; Mocella, M. T. *Inorg. Chem.* **1973**, *12*, 2829.
(26) Atwood, J. L.; Elgamal, H.; Robinson, G. H.; Bott, S. G.; Weeks, J. A.; Hunter, W. E. *J. Inclusion Phenom.* **1984**, *2*, 367.
(27) Bott, S. G.; Elgamal, H.; Atwood, J. L. *J. Am. Chem. Soc.* **1985**, *107*, 1796.

Ultrasound-Promoted Diels-Alder Reactions: Syntheses of Tanshinone IIA, Nortanshinone, and (±)-Tanshindiol B

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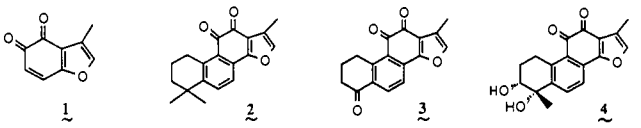
The *o*-quinone abietanoid pigments of the Chinese sage, *Salvia miltiorrhiza* Bunge, are responsible for the broad spectrum of biological activity of the Chinese traditional medicine Dan Shen,[1] prepared from the roots of this species.[2] Many of the active compounds, including secondary metabolites present in only small quantities,[3] can conceivably be prepared by simple Diels-Alder cycloadditions of *o*-quinone **1** with appropriate dienes. Previously

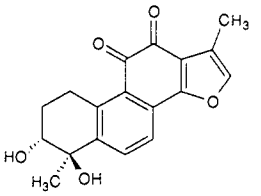


1 **2** **3** **4**

we reported the preparation of **1** and examined its dienophilicity.[4] While **1** was quite reactive with active dienes such as cyclopentadiene, its thermal instability rendered it of limited applicability with more interesting vinylcyclohexene derivatives unless high pressures (11 kbar) were employed. We now report that the cycloadditions can be promoted by ultrasound in the absence of solvent, and we have used this method to synthesize tanshinone IIA (**2**), nortanshinone (**3**), and (±)-tanshindiol B (**4**), active constituents of *S. miltiorrhiza*. This report represents the first example of an ultrasound-promoted Diels-Alder cycloaddition.

The results of the cycloadditions are presented in Table I. The dienes were prepared by the palladium-catalyzed vinyl coupling of tri-*n*-butylvinylstannane with enol triflates as described by Stille (Scheme I).[5] The cycloadditions were best performed in the absence of solvent,[6] though the insolubility of **1** in isoprene (**7**) as well as the volatility of **7** (bp 36 °C) required the use of a solvent (methanol) for this reaction. Increasing amounts of solvent led to decreased yields of cycloadducts (also entry 5, Table I). In a control experiment, heating vinylcyclohexene **5** and *o*-quinone **1** to 45 °C for 2 h did not yield cycloadducts; longer heating (16 h) led only to decomposition of **1**. The cycloadducts were obtained as a mixture of the tetrahydro and dihydro forms. The tetrahydro cycloadducts oxidized to the dihydro compounds upon standing or upon chromatography with silica gel. Stirring the product mixture in oxygen in the presence of silica gel or refluxing with DDQ in benzene yielded the fully aromatized cycloadducts.

The results in Table I indicate that ultrasound is not only effective in promoting the cycloadditions but also improves the regioselectivity. For example, the cycloaddition of diene **10** with **1** in refluxing benzene gave only a 15% yield of cycloadducts in a ratio of 1:1 while sonication of a neat mixture of **10** and **1** gave a 76% yield of cycloadducts with the desired regioisomer, **20** favored 5:1. Deprotection of **20** (Dowex-50, H^+ form, 50% aqueous THF, 70 °C, 12 h) yielded **4**. Cis diol **4** proved to be identical with tanshindiol B, originally assigned the trans structure. Epimerization of the cis diol unit to the trans during deprotection of the acetonide **20** was ruled out by reprotection of synthetic **4** to the identical acetonide **20**. An NOE between the methyl at C-4 and H-3 in the re-formed **20** confirmed the cis stereochemistry of the diol unit. Thus tanshindiol C (**22**), also isolated from *S. miltiorrhiza*, must have the trans diol unit, not the cis as originally assigned.[7]



22

(1) (a) Okumura, Y.; Kakisawa, H.; Kato, M.; Hirata, Y. *Bull. Chem. Soc. Jpn.* **1961**, *34*, 895. (b) Takiura, K.; Koizumi, K. *Chem. Pharm. Bull.* **1962**, *10*, 112. (c) Brieskorn, C. H.; Fuchs, A.; Bredenburg, J. B-son; McChesney, J. D.; Wenkert, E. *J. Org. Chem.* **1964**, *29*, 2293. (d) Baillie, A. C.; Thomson, R. H. *J. Chem. Soc. C* **1968**, 48. (e) Kakisawa, H.; Hayashi, T.; Okazaki, I.; Ohashi, M. *Tetrahedron Lett.* **1968**, 3231. (f) Kakisawa, H.; Hayashi, T.; Yamazaki, T. *Tetrahedron Lett.* **1969**, 301.

(2) According to the Wade-Giles system for Romanizing Chinese characters, the Chinese medicine from *S. miltiorrhiza* Bunge was spelled as "Tan Shen". The current Pin Yin system changes this to "Dan Shen". Reports on biological activity: (a) In *Zhong Cao Yao Xue*, Vol. 3; Nanjing Yao Xue Yuan; "Zhong Cao Yao Xue" Bian Xie Zu, Jiang Su Ren Min Chu Ban She: Nanjing, 1976; pp 947-951. (b) Tong, J. *J. Clin. Dermatol.* **1986**, *4*, 210. (c) In *Pharmacology and Applications of Chinese Materia Medica*; Chang, H. M., But, P. P., Eds.; World Scientific Publishing Co. Pte. Ltd.; Singapore, 1986; Vol. 1, pp 255-268. Also, see ref 3a.

(3) Efforts continue to identify new, active secondary metabolites from Dan Shen since the bioactivities of the purified natural products usually do not match that of the crude medicine itself. (a) Onitsuka, M.; Fujiu, M.; Shinma, N.; Maruyama, H. B. *Chem. Pharm. Bull.* **1983**, *31*, 1670. (b) Kong, D.; Liu, X.; Teng, M.; Rao, Z. *Acta Pharm. Sin.* **1985**, *20*, 747. (c) Luo, H.-W.; Wu, B.-J.; Wu, M.-Y.; Yong, Z.-G.; Niwa, M.; Hirata, Y. *Phytochemistry* **1985**, *24*, 815. (d) Luo, H.-W.; Ji, J.; Wu, M.-Y.; Yong, Z.-G.; Niwa, M.; Hirata, Y. *Chem. Pharm. Bull.* **1986**, *34*, 3166. (e) Lee, A.-R.; Wu, W.-L.; Chang, W.-L.; Lin, H.-C.; King, M.-L. *J. Nat. Prod.* **1987**, *50*, 157. (f) Luo, H. W.; Chen, S.; Lee, J.; Snyder, J. K. *Phytochemistry* **1988**, *27*, 290.

(4) Lee, J.; Tang, J.; Snyder, J. K. *Tetrahedron Lett.* **1987**, *28*, 3427.

(5) (a) Scott, W. J.; Crisp, G. T.; Stille, J. K. *J. Am. Chem. Soc.* **1984**, *106*, 4630. (b) Scott, W. J.; Stille, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 3033. For a recent review, see: Scott, W. J.; McMurry, J. E. *Acc. Chem. Res.* **1988**, *21*, 47.

(6) In a typical procedure, *o*-quinone **1** (100 mg, 0.617 mmol) was placed in a conical reaction vial with the diene (3-5 equiv) and the mixture placed in an ultrasonic cleaner (50/60 kHz, 125 W) for 1-2 h. The temperature was maintained below 45 °C.

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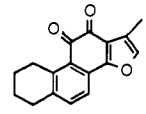
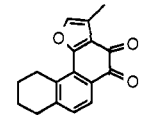
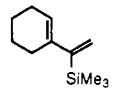
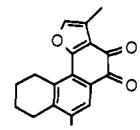
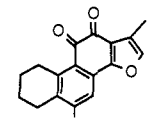
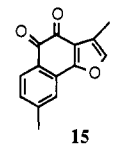
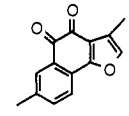
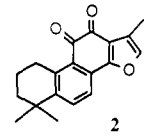
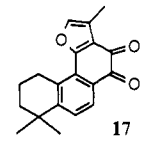
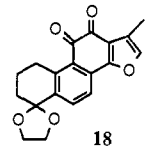
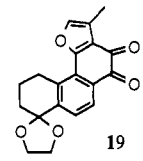
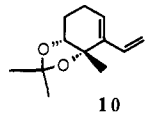
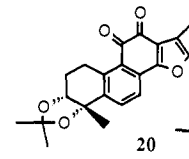
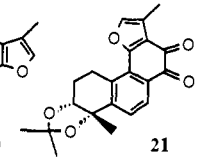
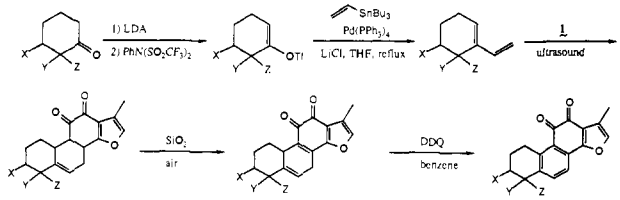
Table I. Cycloadditions of *o*-Quinone (**1**)

entry	dienes	reaction conditions	products	isolated yield[a] (%)
1	 **5**	a. benzene, reflux, 12 hr[b] b. MeOH, reflux, 2 h[b] c. 11 kBar, benzene, rt, 2 h[b] d. $Eu(fod)_3$, 0.08 equiv, benzene reflux, 4h[b] e. ultrasound, neat[c] f. ultrasound, MeOH[c]	 **11**  **12**	(**11**:**12**) a. 45 (2:1) b. 40 (2.5:1) c. 67 (6:1) d. 31 (10:1) e. 65 (7:2) f. 59 (4:1)
2	 **6**	a. benzene, reflux, 12 h[b] b. MeOH, reflux, 4 h[b] c. 11 kBar, MeOH, rt, 2h[b] d. ultrasound, neat[c]	 **13**  **14**	(**13**:**14**) a. 18 (3.5:1) b. 28 (3:2) c. 61 (3.5:1) d. 57 (5:1)
3	 **7**	a. benzene, reflux, 4 h b. ultrasound, MeOH[c]	 **15**  **16**	(**15**:**16**) a. 15 (1:1) b. 38 (5:4)
4	 **8**	a. benzene, reflux, 12 h b. ultrasound, neat[c]	 **2**  **17**	(**2**:**17**) a. 53 (54:45) b. 76 (10:3)
5	 **9**	a. benzene, reflux, 8 h b. 10 kBar, toluene, rt, 45 min c. ultrasound, neat[c] d. ultrasound, toluene, rt, 1 h	 **18**  **19**	(**18**:**19**) a. 18 (1:1) b. 75 (5:2) c. 65 (8:1) d. 17 (4:3)
6	 **10**	a. benzene, reflux, 8 h b. 10 kBar, toluene, rt, 1 h c. ultrasound, neat[c]	 **20**  **21**	(**20**:**21**) a. 15 (1:1) b. 73 (7:1) c. 76[d] (5:1)

[a] Unless otherwise noted, isolated yields are based on the aromatized products. [b] From ref 4. [c] Reaction was carried out at 45 °C for 2 h. [d] The yield based on the dihydro form of **20** and **21**.

Scheme I



In all other cases ultrasound improved, often dramatically, both the yield of cycloadducts and the regioselectivity. The regioisomers were distinguished by three-bond ^1H–^{13}C polarization transfers (selective INEPT)[8] from the aromatic protons ortho to the quinone ring to either the quinone carbonyl or carbon bearing the furan oxygen. As expected, protons of the aromatic ring ortho to a quinone carbonyl oxygen were more deshielded than the protons ortho to the furan oxygen of the other regioisomer.

It is generally accepted[9] that the implosion of the ultrasound-induced cavities results in loci of high pressures (up to 1000 atm) and high temperatures (up to 5000 K).[9b] The reputed high pressures induced by ultrasonication could be responsible for the enhanced reactivity. Indeed, the promotion of the cycloadditions and improvement in the regioselectivity in neat conditions parallel the effect observed with high pressures.[4,10] The observed loss of

(7) The original assignment of the stereochemistry of tanshindiol B and C was based upon the formation of the acetonide of tanshindiol C upon treatment with anhydrous $CuSO_4$ in acetone, conditions under which tanshindiol B was reported not to react. In our hands, authentic tanshindiol B formed acetonide **20** with 2,2-dimethoxypropane (*p*-TsOH, benzene, 4Å molecular sieves, room temperature, 2.5 h) but authentic tanshindiol C did not react under the same conditions, even after 16 h. Finally, stirring either of the two authentic natural products in 0.5 N HCl/THF (1:1) for 12 h did not lead to any detectable epimerization, nor was epimerization detected when **4** was submitted to the acetonide deprotection conditions (Dowex-50, H^+ form, 50% aqueous THF, 70 °C, 12 h).

(8) (a) Bax, A. *J. Magn. Reson.* **1984**, *57*, 314. (b) Bax, A.; Ferretti, J. A.; Nashed, N.; Jerina, D. M. *J. Org. Chem.* **1985**, *50*, 3029.

(9) For recent reviews on sonochemistry, see: (a) Margulis, M. A. *Ultrasonics* **1985**, *23*, 157. (b) Suslick, K. S. In *Modern Synthetic Methods 1986*; Scheffold, R., Ed.; Springer-Verlag: New York, 1986; pp 1–60. (c) Lorimer, J. P.; Mason, T. J. *Chem. Soc. Rev.* **1987**, *16*, 239. (d) Lindley, J.; Mason, T. J. *Chem. Soc. Rev.* **1987**, *16*, 275. (e) Abdulla, R. F. *Aldrichim. Acta* **1988**, *21*, 31.

yield upon the addition of solvent may be due to the reduced pressures from cavity implosion caused by solvent vapor present in the cavities.

In summary, ultrasonication can be a simple, effective method to promote cycloadditions, possibly a substitute for high-pressure conditions. Furthermore, **1** has proven a useful dienophile for the synthesis of several biologically active abietanoid natural products. Thus the reaction of **8** with **1** directly gave **2** (76%, 10:3).[11] Nortanshinone (**3**) was similarly produced from the cycloadduct of **9** and **1** (65%, 8:1) following deprotection by passage through a column of silica gel impregnated with $FeCl_3$.[12] Synthetic compounds (**2**, **3**, and **4**) were identical with authentic samples.[3c,13]

Acknowledgment. We thank the Camille and Henry Dreyfus Foundation, the donors of the Petroleum Research Fund, administered by the American Chemical Society, the Research Corp., and the National Institutes of Health (Grant GM-38014) for support. We also thank Professor Hou Wei Luo of the Nanjing College of Pharmacy for providing authentic samples of **2**, **3**, **4**, and **22** and Francis J. Hannon for assistance in running the high-pressure reactions.

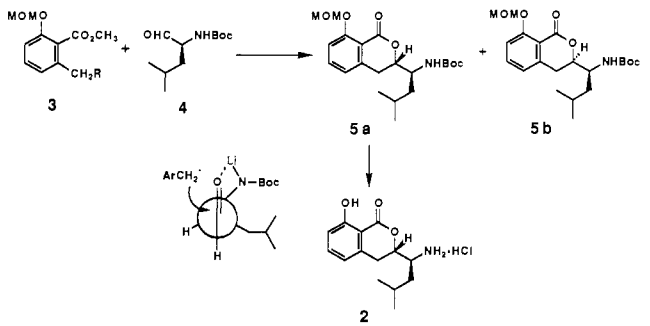
(10) The ratio of cycloadduct regioisomers reported in ref 4 for diene **6** was inadvertantly reversed.

(11) Previous syntheses of **2** and related natural products from *S. miltiorrhiza*: (a) Baille, A. C.; Thomson, R. H. *J. Chem. Soc. C* **1968**, 48. (b) Kakisawa, H.; Inouye, Y. *J. Chem. Soc., Chem. Commun.* **1968**, *1327*. (c) Kakisawa, H.; Tateishi, M.; Kusumi, T. *Tetrahedron Lett.* **1968**, 3783. (d) Inouye, Y.; Kakisawa, H. *Bull. Chem. Soc. Jpn.* **1969**, *42*, 3318. (e) Imai, S. *J. Sci. Hiroshima Univ., Ser. A* **1971**, *35*, 171. (f) Tateishi, M.; Kusumi, T.; Kakisawa, H. *Tetrahedron* **1971**, *27*, 237. (g) Huot, R.; Brassard, P. *Can. J. Chem.* **1974**, *52*, 88.

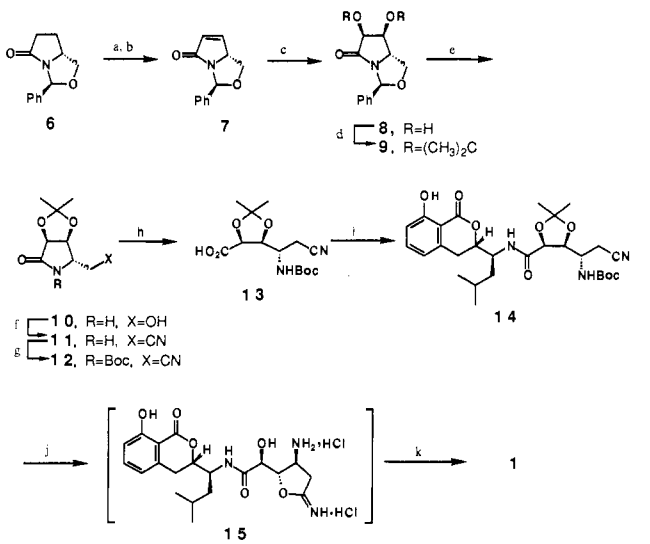
(12) (a) Kim, K. S.; Song, Y. H.; Lee, B. H.; Hahn, C. S. *J. Org. Chem.* **1986**, *51*, 404. (b) Fadel, A.; Yefsah, R.; Salaun, J. *Synthesis* **1987**, 37.

(13) Chien, M.-K.; Young, P.-T.; Ku, W.-H.; Chen, Z.-X.; Chen, H.-T.; Yeh, H.-C. *Acta Chim. Sin.* **1978**, *36*, 199.

Scheme I



Scheme II[a]



[a] Reagents and conditions: (a) 1.3 equiv of LDA, THF, −70 °C, 0.5 h; then 1.2 equiv of PhSeBr (prepared in situ from Ph_2Se_2 and Br_2), THF, −70 °C, 15 min; (b) ozone, CH_2Cl_2, −74 °C, 2 h; pyridine, −74 °C → room temperature, 75% from **6**; (c) 0.1 equiv of OsO_4, 1.4 equiv of NMO, aqueous acetone, room temperature, 15 h, 65%; (d) an excess of 2,2-dimethoxypropane, PPTS (cat.), acetone, room temperature, 10 h, 98%; (e) 5% Pd–C, NH_2NH_2·H_2O, MeOH, 95%; (f) 2 equiv of KCN, 0.1 equiv of 18-crown-6, 1.1 equiv of Bu_3P, 1.1 equiv of CCl_4, CH_3CN, 30–40 °C, 1 h; then 70–80 °C, 2 h, 71%; (g) 1.15 equiv of $(Boc)_2O$, DMAP (cat.), CH_3CN, room temperature, 1 h, 92%; (h) LiOH, 70% aqueous THF, room temperature, 30 min, 70%; (i) **2**, 1.25 equiv of DEPC, 3.2 equiv of Et_3N, DMF, 0 °C, 3 h, room temperature, 20 h; then an additional 0.45 equiv of DEPC, room temperature; an additional 1.47 equiv of Et_3N, room temperature, 11 h, 70%; (j) an excess of trimethyl orthoformate, 5% HCl–MeOH, 5 °C, 44.5 h; (k) H_2O, 12 h; 0.1 N NaOH (pH 9), aqueous MeOH, room temperature, 3 h; 0.1 N HCl (pH 6.5), 76% from **14**.

Stereoselective Total Synthesis of AI-77-B, a Gastroprotective Substance from *Bacillus pumilus* AI-77[1,2]

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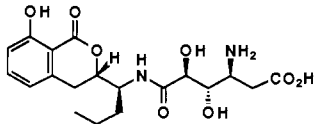
Received October 11, 1988

AI-77-B (**1**),[3] isolated from a culture broth of *Bacillus pumilus* AI-77 as the major product with characteristic fluorescence, is a unique naturally occurring 3,4-dihydroisocoumarin derivative having a hydroxy amino acid side chain.[4] Its absolute stereostructure containing *S* configurations at all five chiral centers has been established by Shimojima and co-workers[3] through X-ray analysis in combination with chemical and spectral studies. AI-77-B has been found to exhibit potent antiulcerogenicity action without central suppressive, anticholinergic, and antihistaminergic properties.[3b,5] We wish to report the first synthesis of AI-77-B (**1**) in a stereoselective and convergent manner, which provides an easy access to many other congeners required for pharmacological evaluation.[6]



1 (AI-77-B)

(1) "New Methods and Reagents in Organic Synthesis. 83". For Part 82, see: Kawai, A.; Hara, O.; Hamada, Y.; Shioiri, T. *Tetrahedron Lett.* **1988**, *29*, 6331.

(2) Presented in part at the 11th International Congress of Heterocyclic Chemistry, Heidelberg, Aug 16–21, 1987 (*Abstracts of Papers*, p 178) and at the 108th Annual Meeting of the Pharmaceutical Society of Japan, Hiroshima, April 4–6, 1988 (*Abstracts of Papers*, S. 61 and p 49).

(3) (a) Shimojima, Y.; Hayashi, H.; Ooka, T.; Shibukawa, M.; Iitaka, Y. *Tetrahedron Lett.* **1982**, *23*, 5435. (b) Shimojima, Y.; Hayashi, H.; Ooka, T.; Shibukawa, M. *Agric. Biol. Chem.* **1982**, *46*, 1823. (c) Shimojima, Y.; Hayashi, H.; Ooka, T.; Shibukawa, M. *Tetrahedron* **1984**, *40*, 2519.

(4) Structurally analogous compounds are known; see: (a) Okazaki, H.; Kishi, T.; Beppu, T.; Arima, K. *J. Antibiot.* **1975**, *28*, 717. (b) Ito, J.; Omoto, S.; Shomura, T.; Nishizawa, N.; Miyado, S.; Yuda, Y.; Shibata, U.; Inoue, S. *J. Antibiot.* **1981**, *34*, 611. (c) Ito, J.; Shomura, T.; Omoto, S.; Miyado, S.; Yuda, Y.; Shibata, U.; Inoue, S. *Agric. Biol. Chem.* **1982**, *46*, 1255. (d) Ito, J.; Omoto, S.; Nishizawa, N.; Kodama, Y.; Inoue, S. *Agric. Biol. Chem.* **1982**, *46*, 2659.

(5) Shimojima, Y.; Hayashi, H. *J. Med. Chem.* **1983**, *26*, 1370.

(6) Since AI-77-B has been transformed to AI-77-C, -D, and -F,[3a,c] this synthesis constitutes a formal synthesis of these congeners.

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