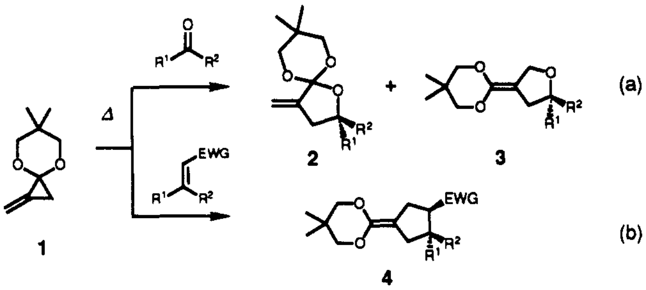
Scheme I

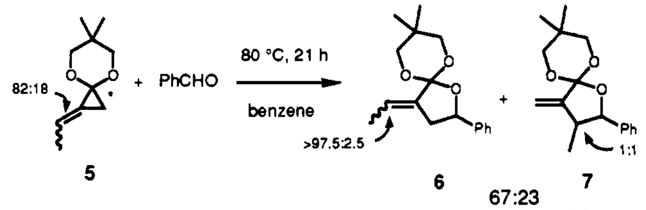


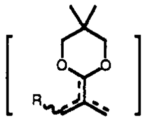
faster with 1 than aliphatic derivatives (entries 5, 6, and 8–10). Aldehydes reacted smoothly below 100 °C, while more sterically encumbered ketones reacted more slowly, requiring higher temperatures (100–130 °C). In these latter cases, use of high pressure proved particularly rewarding as shown in entry 10 for the cycloaddition of 4-*tert*-butylcyclohexanone, which was complete at 80 °C under 13–14 kbar of pressure. This cycloaddition took place selectively from the electronically favored axial direction,[5] and the stereoselectivity (80:20) remained unchanged under high-pressure conditions (cf. entries 9 and 10).

Whereas the cycloaddition of α,β-unsaturated *ketones* took place highly rgioselectively on the olefin[3] (Scheme I, reaction b), the cycloaddition to α,β-unsaturated *aldehydes* gave a product mixture due to competing cycloadditions to the carbonyl and the olefinic groups[3] (entry 11). The relative rates of these two paths, as examined for several enals, were found to fall in a range of 1:2 to 2:1.

Brief studies of competitive kinetic experiments confirmed the nucleophilic nature of this cycloaddition.[6] Thus, the rate of the cycloaddition doubled as the aldehyde acceptor was changed first from *p*-anisaldehyde to benzaldehyde, and then again on changing to *p*-chlorobenzaldehyde. Perfluorobenzaldehyde (entry 4) was the most reactive among the carbonyl compounds examined.

The reaction of an ethylidene compound 5 brings up the important issue of the regiochemical course of the cycloaddition. Thus, 5,[7] prepared through the same synthetic sequence used for 1,[3] was subjected to the reaction with benzaldehyde. Most interestingly, the reaction predominantly gave an ethylidene lactone acetal 6[7] (57% isolated yield) together with a methylene lactone 7 (28%). The formation of 6 requires that the starred C–C bond in 5 be cleaved *prior to* the coupling with the aldehyde. An important consequence of such a cleavage is the formation of a trimethylenemethane 8 (R = Me).[8] A mechanistic possibility that the present cycloaddition proceeds through a trimethylenemethane[9] is certainly consistent with a variety of experimental observations including the acceptor-dependent dichotomy of the reaction paths (i.e., C=O vs C=C; Scheme I). This fascinating mechanism is being actively investigated.





8

Acknowledgment. We thank the Ministry of Education, Science, and Culture for financial support (Grant-in-Aid for Scientific Research). We thank Prof. B. M. Trost for providing authentic spectra for structural assignments.

Supplementary Material Available: Physical data for the cycloadducts and structural assignment of the adduct in entries 9 and 10 in Table I (9 pages). Ordering information is given on any current masthead page.

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[5] The trimethylenemethane-type intermediate by Trost gives a cycloadduct due to an equatorial approach of the reagent (ref 2a).

[6] (a) The nucleophilic nature of 1 has also been ascertained in the cycloaddition to olefins (ref 3). (b) Attempted cycloaddition of 1 to a benzaldehyde imine failed.

[7] The compounds 5 and 6 consisted of one major geometrical isomer. The stereochemistry has not been determined yet.

[8] (a) Interconversion between a methylenecyclopropane and a trimethylenemethane is a well-established process. Cf.: Ullmann, E. F. *J. Am. Chem. Soc.* **1960**, *82*, 505. Gajewski, J. J. *J. Am. Chem. Soc.* **1971**, *93*, 4450. Doering, W. v. E.; Birladeanu, L. *Tetrahedron* **1973**, *29*, 449. Gilbert, J. C.; Butler, J. R. *J. Am. Chem. Soc.* **1970**, *92*, 2168. Gilbert, J. C.; Higley, D. P. *Tetrahedron Lett.* **1973**, 2075. Kirmse, W. Murawski, H.-R. *J. Chem. Soc., Chem. Commun.* **1977**, 122. Salinaro, R. F.; Berson, J. A. *J. Am. Chem. Soc.* **1982**, *104*, 2228. Goldschmidt, Z.; Finkel, D. *J. Chem. Soc., Perkin Trans. 1* **1983**, 45. Buchwalter, S. L. *Tetrahedron* **1984**, *40*, 5097. Creary, X.; Mehrsheikh-Mohammadi, M. E. *J. Org. Chem.* **1986**, *51*, 2664. LeFevre, G. N.; Crawford, R. J. *J. Org. Chem.* **1986**, *51*, 747. Baldwin, J. E.; Ghatlia, N. D.; Lundbäck, K. M. O. *Acta Chem. Scad. B* **1987**, *41*, 698. Molchanov, A. P.; Kostikov, R. R. *Zh. Org. Khim*, **1988**, *24*, 949. (b) Theoreticl studies: Hehre, W. J.; Salem, L.; Wilcott, M. R. *J. Am. Chem. Soc.* **1974**, *96*, 4328. Feller, D.; Tanaka, K.; Davidson, E. R.; Borden, W. T. *J. Am. Chem. Soc* **1982**, *104*, 967. Skancke, A.; Schaad, L. J.; Hess, B. A., Jr. *J. Am. Chem. Soc.* **1988**, *110*, 5315. Review: Akiba, K. J. *Synth. Org. Chem. Soc. Jpn.* **1973**, *31*, 635. (c) Very facile degenerate rearrangement of a suitably labeled derivative of 1 suggests facile generation of 8 under the present conditions: unpublished results.

[9] Berson's trimethylenemethane species (Berson, J. A. *Acc. Chem. Res.* **1978**, *11*, 486) undergoes cycloaddition only to benzaldehyde and to a tricarbonyl compound: Little, R. D. *Chem. Rev.* **1986**, *86*, 875.

1,2-Functionalization of α,β-Epoxycycloalkanones

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Summary: For 1,2-functionalization, α,β-epoxy cycloalkanones were treated with 2.1 equiv of 2-lithio-2-(trimethylsilyl)-1,3-dithiane to give high yields of *trans*-2-dithianyl-3-dithianylidene-1-cycloalkanols, which were oxidatively hydrolyzed with an excess of halogenating agents in alcohols to the corresponding acetal esters.

Our synthetic approaches to aglycons of anthracyclines such as daunomycinone (1) and adriamycinone (2)[1] involve

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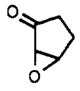
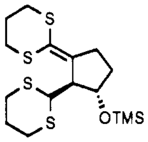
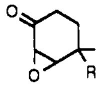
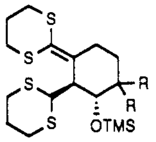
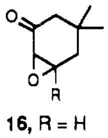
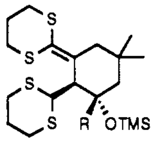
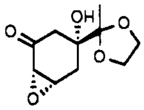
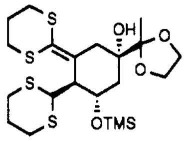
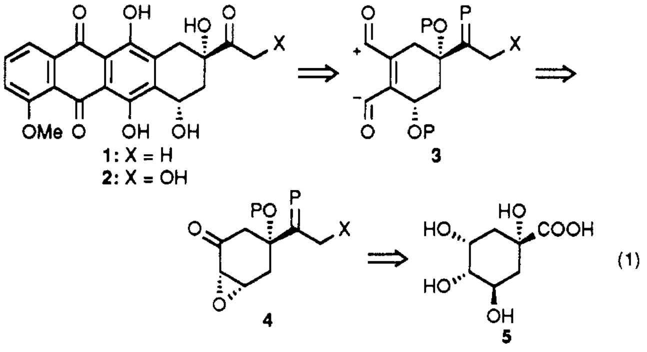
[1] For representative reviews, see: (a) Kelly, T. R., Ed. *Tetrahedron* **1984**, *40*, 4539–4793. (b) Krohn, K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 790.

Table I. 1,2-Functionalization of α,β-Epoxycycloalkanones with 2-Lithio-2-(trimethylsilyl)-1,3-dithiane

entry	substrate	reactn temp[a] (°C)	product[b]	yield (%)[c]
1	 **12**	−78	 **13**	86
2	 **7**, R = H	−78	 **9**, R = H	99
3	**14**, R = Me	0	**15**, R = Me	42
4	 **16**, R = H	−78	 **17**, R = H	78
5	**18**, R = Me	0	**19**, R = Me	62
6	 **20**[d]	−78	 **21**	76

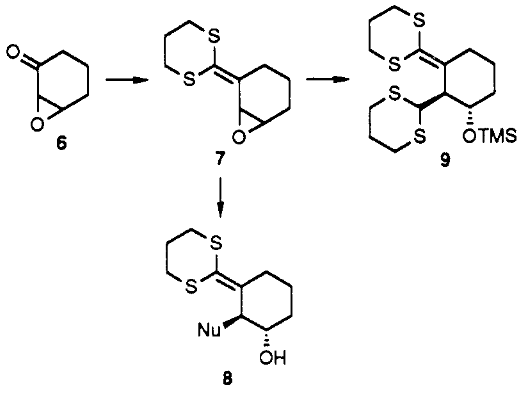
[a] The epoxy ketone was added to a stirred THF solution of 2-lithio-2-(trimethylsilyl)-1,3-dithiane (2.1 equiv except for the case of entry 6 (3 equiv)) at −78 °C. The reaction was complete in 1 h in all cases. [b] Substantiated by IR, mass, and NMR spectra and combustion analyses. [c] Based on isolated product, homogenous by TLC and NMR. [d] Prepared from (−)-quinic acid in six steps. Details will be reported later.

preparation of enantiomerically pure[2] 1,4-dipole **3**[3] and coupling with a juglone derivative (as a CD ring portion) to produce the tetracyclic systems. The conceptual 1,4-dipole **3** having all functionality and stereochemistry required for the A ring of daunomycinone might be prepared by 1,2-functionalization of α,β-epoxycyclohexanone derivative **4**, which in turn would be prepared from the readily available (−)-quinic acid (**5**) (eq 1). With the success of the latter task, which will be reported in due course, efforts were made to functionalize α,β-epoxy ketones in a 1,2 sense, which is the subject of the present report.



(1)

Initially, a model substrate, α,β-epoxycyclohexanone (**6**), was treated with 1.0 equiv of 2-lithio-2-(trimethylsilyl)-1,3-dithiane[4] in order to produce the corresponding ketene dithioketal **7**,[5] which might have been further elaborated to **8** by addition of a one- or two-carbon nucleophile at the allylic methine carbon of the oxirane ring. However, regardless of the amount of the reagent used, allylic epoxide **7** was not observed. Instead, bis(dithiane) silyl ether **9** was obtained in all cases (eq 2).



(2)

Another reaction with 2.1 equiv of the lithiodithiane at −78 °C in tetrahydrofuran (THF) provided silyl ether **9** in almost quantitative yield. The stereochemistry of adduct **9** was judged to be trans by the coupling constants

---

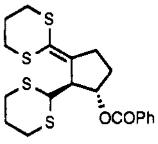
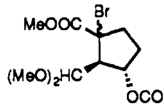
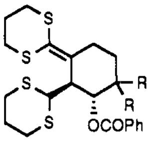
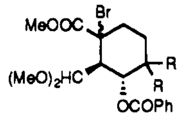
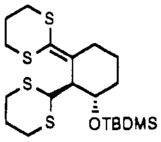
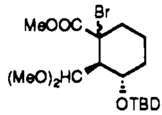
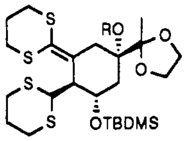
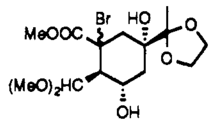
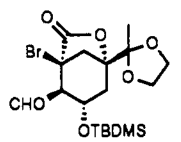
(2) For a recent asymmetric synthesis using a enantiomerically pure starting material, see: (a) Krohn, K.; Rieger, H. *Liebigs Ann. Chem.* **1987**, 515. (b) Natura, Y.; Nishigaichi, Y.; Maruyama, K. *J. Chem. Soc., Chem. Commun.* **1989**, 1203.

(3) For representative 1,4-diple equivalents, see: (a) Swenton, J. S.; Freskos, J. N.; Morrow, G. W.; Sercel, A. D. *Tetrahedron* **1984**, *40*, 4625. (b) Russell, R. A.; Irvine, R. W.; Warrener, R. N. *J. Org. Chem.* **1986**, *51*, 1595. (c) Chenard, B. L.; Dolson, M. G.; Sercel, A. D.; Swenton, J. S. *Ibid.* **1984**, *49*, 318. (d) Freskos, J. N.; Morrow, G. W.; Swenton, J. S. *Ibid.* **1985**, *50*, 805. (e) Kraus, G. A.; Cho, H.; Crowley, S.; Roth, B.; Sugimoto, H.; Prugh, S. *Ibid.* **1983**, *48*, 3439. (f) Tamura, Y.; Akai, S.; Kishimoto, H.; Kirihara, M.; Kita, Y. *Tetrahedron Lett.* **1987**, *28*, 4583.

(4) (a) Grobel, B.-T.; Seebach, D. *Synthesis* **1977**, 357. (b) Seebach, D.; Kolb, M.; Grobel, B.-T. *Chem. Ber.* **1973**, *106*, 2277. (c) Carey, F. A.; Court, A. S. *J. Org. Chem.* **1972**, *37*, 1926. (d) Seebach, D.; Corey, E. J. *Ibid.* **1975**, *40*, 231.

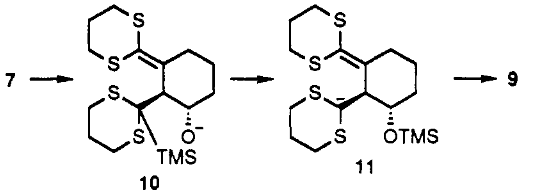
(5) For some unknown reasons, *acyclic* α,β-epoxy ketones gave complex mixtures.

Table II. Oxidative Hydrolysis of Bis(dithiane) 23[a]

entry	substrate	method[b]	solvent (temp, °C)	product (yield,[c] %)
1	 **25**	A	MC-MeOH[d] (23)	 **26** (92)
2	 **27**, R = H	A	MC-MeOH[d] (23)	 **28**, R = H (90)
3	**29**, R = Me	A	MC-MeOH[d] (40)	**30**, R = Me (88)
4	 **31**	B	MC-MeOH[d] (0)	 **32** (86)
5	 **33**, R = H	B	95% MeOH(0)	 **34** (81)
6	**35**, R = TMS	D	MeOH(0)	**34** (53)
7	**33**, R = H	C	wet THF(0)	 **36** (61)
8	**35**, R = TMS	B	wet MeCN(0)	**36** (41)

[a] Br_2 or NBS was added to a stirred solution of substrate and an acid scavenger, if any, at 0 °C. All reactions were complete within 30 min at the temperature shown. [b] A, NBS (7 equiv); B, Br_2 (10 equiv) $-CaCO_3$ (10 equiv); C, NBS (10 equiv); D, Br_2 (12 equiv) $-Et_3N$ (19 equiv). [c] The yield is based on the purified diastereomer (approximately 1:1 in every case) products (usually unstable), the identity of which was confirmed by NMR, IR, and mass spectra and combustion analyses, where applicable. [d] Methylene chloride/methanol = 7:3.

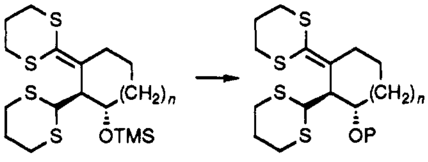
of the methine protons (J = 11.2–11.6 Hz) and NOE effects of NOESY spectra. Presumably, the allylic epoxide **7**, which has sulfur atoms with unshared electrons at the allylic unit, is reactive enough to undergo rapid further reaction with the excess lithiodithiane even at −78 °C. Subsequent silyl migration from carbon to oxygen[6] would furnish silyl ether **9** (eq 3). Unfortunately, however, attempts to capture the carbanion **11** in situ with one-carbon electrophiles under various conditions were not fruitful.



(3)

Since our original objective was realized with the model compound in an unexpected but novel manner, other α,β-epoxycycloalkanones were treated with the dithiane reagent under the standard condition, the results of which are shown in Table I.

For the subsequent conversions in which the two dithianyl groups were to be differentiated, the silyl ether of **22** was deprotected with tetra-*n*-butylammonium fluoride in THF at 23 °C, and the resulting free hydroxyl group was protected with benzoyl chloride (pyridine, 0 °C) to the benzoate **23a**, or with *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBDMSOTf, CH_2Cl_2, 0 °C) to the corresponding silyl ether **23b** in high yield (eq 4).



22

23a: P = COPh
23b: P = TBDMS

(4)

One such conversion would be oxidative hydrolysis of the bis(dithiane) moiety in **23** to the halogenated acetal ester **24**. Since anthracycline precursor **21** or its derivatives would contain acid-labile groups, numerous reactions were conducted to achieve the selective conversions under mild conditions[4] (eq 5).

It was found that the bis(dithiane) compounds **23** react with *N*-bromosuccinimide (NBS) or Br_2 (7–10 equiv) in a solvent mixture containing alcohol and an acid scavenger

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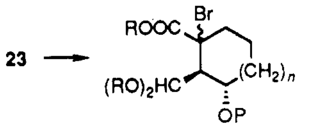
[6] For precedents for silyl migration from carbon to other hetero atoms, see: Ager, D. J. *Synthesis* **1984**, 384.



(5)

24

in cases of the silyl ethers to provide approximately 1:1 diastereomeric mixtures of the corresponding bromo acetal esters **24** in high yields (Table II). The stereochemical outcome of the newly created sp^3 chiral center in the acetals **24** is inconsequential since the chirality at the carbon will be eventually eliminated in our projected synthesis. However, in the absence of nucleophilic solvents, the anthracycline precursors **33** and **35**, regardless of protection of the tertiary hydroxyl group, gave γ-lactone **36** (Table II, entries 7 and 8).

With enantiomerically pure acetal ester **34** and lactone **36** now secured by 1,2-functionalization of α,β-epoxy ketones through double dithiane addition and simple oxidative hydrolysis, efforts are being made to convert them to a 1,4-dipole equivalent for the subsequent condensation with a juglone derivative.

Acknowledgment. Financial support from the Korea Science and Engineering Foundation and the Organic Chemistry Research Center are appreciated.

Supplementary Material Available: Experimental procedures and spectral data of products and NMR spectra of compounds **30** and **36** (22 pages). Ordering information is given on any current masthead page.

Selective Functionalization in the Bay Region of Polycyclic Aromatic Hydrocarbons via Dilithiation

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Received June 25, 1990

Summary: Sequential reaction of polycyclic aromatic hydrocarbons with butyllithium/TMEDA hexane and electrophiles allows preparation of derivatives functionalized in the bay region.

Several *cis,cis*-1,4-dilithiobutadiene derivatives **1** are known to adopt a symmetrical bridged structure **2** in the solid state.[1-3] Calculations indicate that structure **2** is highly stabilized in comparison to possible nonbridged geometries.[4-6] Schleyer and co-workers have demonstrated that this double lithium bridging can provide the thermochemical driving force for the otherwise surprising ortho-dilithiation of biphenyl (**3** → **4**) by *n*-BuLi in TMEDA/hexane.[7] A number of related lithium-directed metalations of aromatic compounds have been studied in detail.[8,9] We report here on the extension of this method to polycyclic aromatic hydrocarbons (PAH's). This procedure allows selective functionalization in the bay region of PAH's and can be used to prepare useful heterocycles efficiently.

1

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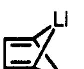

2

3

4

Table I. Relative Concentrations (%) of Deuterated PAH's after Sequential Reaction with BuLi/TMEDA and D$_2$O

compound	d_0[a]	d_1[a]	d_2[a]	d_3[a]	d_4[a]	portion of d in Bay Region[b,c]
triphenylene (5)	2.5	12.3	60.6	23.9	0.7	85
phenanthrene (10)	0.9	12.8	64.4	19.0	2.9	41
chrysene (11)	0.9	10.7	69.5	18.3	0.6	62

[a] Determined by analysis of the appropriate EI mass spectral m/e values. Corrections were made for M − 1, M − 2 values, assuming random loss of d. See: Westmore, J. B.; Reimer, M. L. J.; Charlton, J. *Spectrosc: Int. J.* 1982, *1*, 86. [b] Determined from integration of appropriate signals in the ^{2}H NMR spectra. [c] The bay positions are defined as C_1,C_{12} of **5** and C_4,C_5 of **10** and **11**.

Thus, the reaction of triphenylene **5** with 5 equiv of *n*-butyllithium in TMEDA/hexane at 60 °C for 3 h gave a red solution of lithio derivatives. Quenching with D_2O afforded 95% of triphenylene which is predominantly d_2 although significant quantities of d_1 and d_3 were also present (see Table I). ^{2}H NMR spectroscopy indicates that 85% of the D is in the α-position.[10] Quenching the lithiation mixture with SCl_2 gives the known triphenyleno[4,5-*bcd*]thiophene **8**.[11] Purification[12] through oxidation with H_2O_2/HOAc to the unisolated sulfone, and column chromatographic separation from nonpolar impurities followed by reduction with $LiAlH_4$/THF allowed isolation of **8** in 53% yield. These data establish that 1,12-dilithiotriphenylene **6** is the major lithiated species.

Quenching **6** with I_2 afforded 30% of 1,12-diiodotriphenylene **9** as pale yellow crystals, mp 238–40 °C. The mass spectrum and the symmetrical ^{1}H NMR spectrum indicated structure **9**.[13] Since molecular mechanics calculations (SYBYL MAXIMIN2)[14] suggest that the aromatic rings of **9** should show gross distortions from pla-

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(1) Schubert, U.; Neugebauer, W.; Schleyer, P. v. R. *J. Chem. Soc., Chem. Commun.* **1982**, 1184.

(2) An X-ray structure of the tetraphenyl derivative of 1 shows this bridged structure: Schleyer, P. v. R., private communication.

(3) Setzer, W. N.; Schleyer, P. v. R. *Adv. Organomet. Chem.* **1985**, *24*, 353.

(4) Kos, A. J.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1980**, *102*, 7928.

(5) Schleyer, P. v. R. *Pure Appl. Chem.* **1983**, *55*, 355; **1984**, *56*, 151.

(6) Also see: Streitwieser, A., Jr.; Swanson, J. T. *J. Am. Chem. Soc.* **1983**, *105*, 2502. Streitwieser, A., Jr. *Acc. Chem. Res.* **1984**, *17*, 353.

(7) Neugebauer, W.; Kos, A. J.; Schleyer, P. v. R. *J. Organomet. Chem.* **1982**, *228*, 107.

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(13) **9**: MS m/e 456 (M^+ for $C_{18}H_{10}I_2$); H NMR ($CDCl_3$) 7.28 (t, J = 7.7 Hz, 2 H), 7.60 (sym. m, 2 H), 8.01 (d, J = 7.5 Hz, 2 H), 8.40 (sym. m, 2 H), 8.43 (d, J = 7.8 Hz, 2 H).

(14) SYBYL version 5.3, Triplos Assoc., St. Louis, MO.

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