The Synthesis of Novel Polycyclic Heterocyclic Ring Systems. 2 [1]. Naphtho[2,1-b:4,3-g]bisbenzo[b]thiophene

Kenji Sasaki [2], Osamu Tokuda, and Takashi Hirota

Faculty of Pharmaceutical Sciences, Okayama University, Tsushima, Okayama 700, Japan

Jiann-Kuan Luo and Raymond N. Castle* [2]

Department of Chemistry, University of South Florida, Tampa, FL 33620-5250, U.S.A.
Received March 22, 1996

Dedicated to the memory of Professor Nicholas Alexandrou

The novel polycyclic heterocyclic ring system, naphtho[2,1-b:4,3-g]bisbenzo[b]thiophene was synthesized from 5-[2-(2-bromo-3-thienyl)ethenyl]naphtho[2,1-b][1]benzothiophene. The assignment of its ^{1}H and ^{13}C nmr spectra was also accomplished by utilizing two-dimensional nmr methods.

We have been interested in the synthesis of novel polycyclic heterocyclic ring system *via* photocyclization of the appropriate enamide and to study their spectroscopic properties [3]. In that photocyclization, the chlorine substituent at the α-position of the acyl group of the enamide acted as a potential leaving group and obviated the need for an oxidant to generate the aromatic lactam. On the other hand, we have already reported several novel angular polycyclic aromatic thiophenes containing two thiophene rings with a molecular weight 340 as part of the study directed toward providing all of the possible polycyclic thiophenes suspected of occurring in coal liquids, shale oil, or related coal derived products [4]. However, in those cases, the desired compounds were synthesized by the photocyclization under oxidizing conditions using iodine and air as the oxidants.

In this paper we describe the novel angular polycyclic aromatic bisthiophene ring, that is, naphtho[2,1-b:4,3-g]bisbenzo[b]thiophene (6) by photocyclization under non-oxidizing conditions without using iodine. The total assignments of the ^{1}H and ^{13}C nmr spectra of compound 6 were also determined.

The synthetic pathway to compound 6 is illustrated in Scheme 1 and we employed 5-[2-(2-bromo-3-thienyl)-ethenyl]naphtho[2,1-b][1]benzothiophene (5) as a key intermediate for the non-oxidizing photocyclization. 2-Bromo-3-bromomethylthiophene (2) was prepared in a similar manner to that of Archer *et al.* [5]. Compound 2 was converted to diethyl (2-bromo-3-thenyl)phosphonate (3) by the method of Guillaume *et al.* [6]. This crude phosphonate 3 was condensed with naphtho[2,1-b][1]benzothiophene-5-

Scheme 1
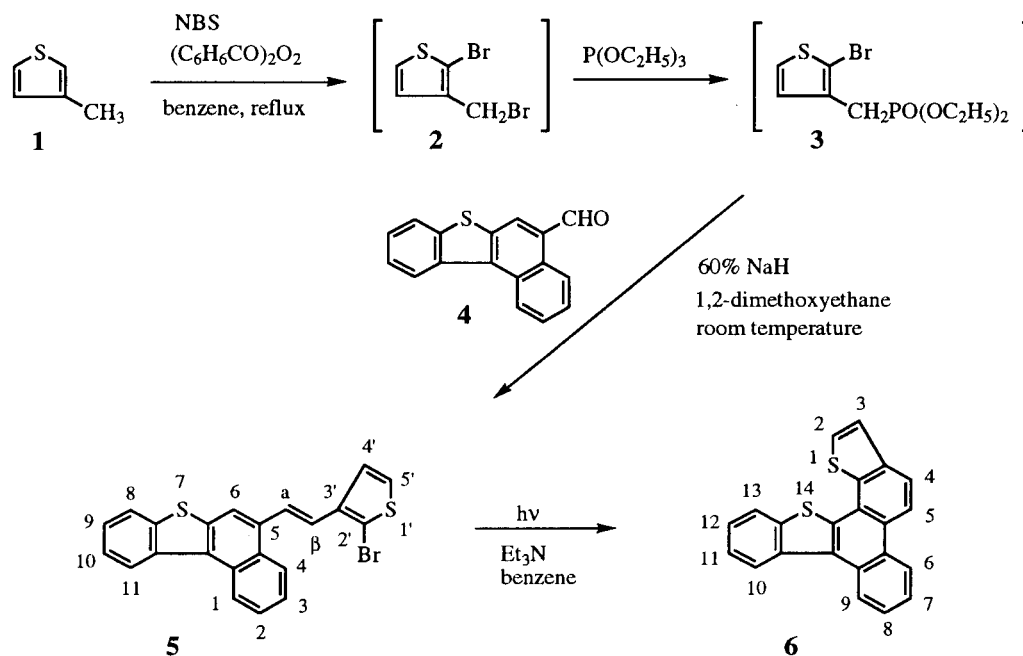
carbaldehyde (**4**) [1] under Wadsworth-Emmons conditions using sodium hydride as the base to give **5** in 18% overall yield from 3-methylthiophene (**1**). In the EI-mass spectrum of **5**, a molecular ion was observed at m/z 420 accompanied by a ($M^+ + 2$) peak of almost equal intensity. Elemental analysis and the assignment of the [1]H-nmr spectrum of **5** (see Figure 1) established the structure of **5**. Irradiation of **5** in benzene solution containing triethylamine with a 500 watt high pressure mercury vapor lamp gave the desired cyclization product **6** in 34% yield. In comparison with the yield (32%) of phenanthro[1,2-*b*]thiophene obtained by photocyclization under oxidizing conditions using iodine in a previous paper [4], the introduction of a bromine substituent on the thiophene ring in the photocyclization under non-oxidizing conditions did not improve the yield.

NMR Spectroscopy.

Assignment of **5**.

The ^{1}H nmr spectrum of **5** shows one singlet, two two-spin systems, and two four-spin systems which allows

the assignment from the ^{1}H-^{1}H COSY using a pulsed field gradient probe (^{1}H-^{1}H pfg-COSY) spectrum (Figure 1). From the [1]H-nmr spectrum one can see two doublets resonating at 7.20 ppm and 7.80 ppm which have a relatively large coupling constant (16 Hz). Considering steric hindrance and the coupling constants of a *cis*-vicinal proton (usually 6-12 Hz) and *trans*-vicinal proton (usually 12-18 Hz) of ethylene derivatives, these two doublets can be assigned as α- and β-protons of the *trans*-(2-bromo-3-thienyl)ethenyl moiety of **5**. The other two doublets resonating at 7.31 ppm (J = 5.8 Hz) and 7.35 ppm (J = 5.8 Hz) should be assigned as H4' and H5' because H2 and H3 of thiophene are usually observed at 7.20 ppm and 6.96 ppm, respectively, and their coupling constants are 4.8 Hz [7]. One proton singlet was easily assigned as H6. From the ^{1}H-^{1}H pfg-COSY spectrum, two four-spin systems could be seen. One of them included protons resonating at 9.03 ppm, 7.74 ppm, 7.61 ppm, and 8.31 ppm. The other four-spin system included protons at 8.81 ppm, 7.58 ppm, 7.48
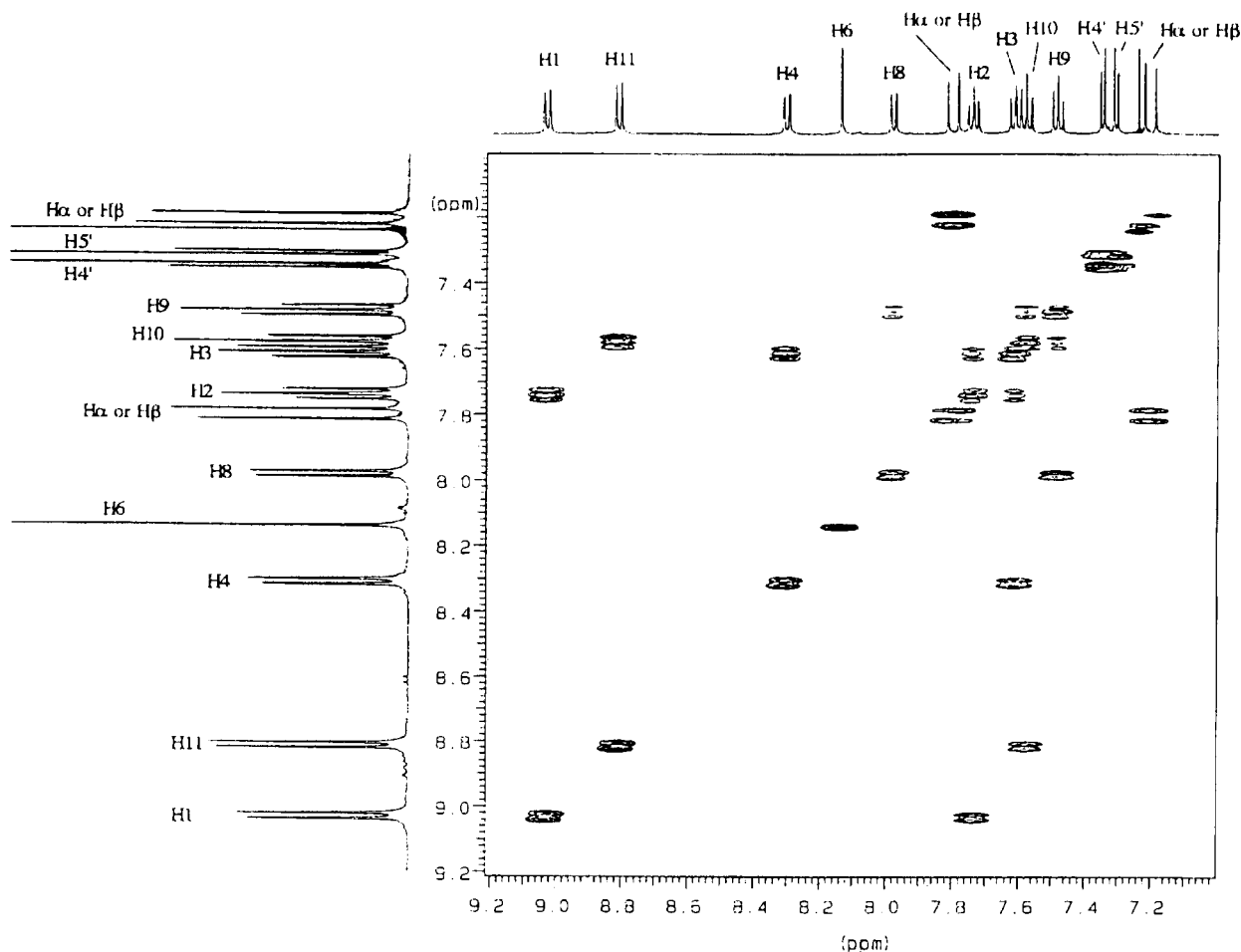

Figure 1. ^{1}H-^{1}H pfg-COSY Spectrum of **5**.

ppm, and 7.98 ppm. Considering the structure of **5**, the two protons, H1 and H11, should resonate at lower field because they are bay-region protons. Therefore two low field protons resonating at 9.03 ppm and 8.81 ppm, which are respectively recognized as a terminated proton in the ^{1}H-^{1}H pfg-COSY spectrum, will be assigned as H1 and H11, however, one can not decide which proton is which at this stage. The remaining two terminal protons are signals resonating at 8.31 ppm and 7.98 ppm. Between these protons, we assigned the signal at 7.98 ppm as H8 because H7 of the non-substituted benzo[b]thiophene usually resonated around 7.9 ppm [7] and there is no factor to change the chemical shift of the proton at the same site (H8) except for the solvent effect in the case of **5**. The other terminal proton resonating at 8.81 ppm in the same four-spin system including H8 is therefore assigned as H11. Between the two triplet protons in the same four-spin system, the signal resonating at 7.58 ppm is coupled with H11 but not with H8 and the signal resonating at 7.48 ppm is coupled with H8 and

not with H11. Therefore the former signal at 7.58 ppm can be assigned as H10 and the latter as H9. In the remaining four-spin system, the lowest field signal at 9.03 ppm is assigned as H1 because one of two bay-region protons was assigned as H11 as described above. The other terminal proton at 8.31 ppm in the same four-spin system including H1 is automatically assigned as H4. Finally one of the remaining two triplet protons resonating at 7.74 ppm is assigned as H2 because of the correlation with H1 and non-correlation with H4, and the other proton resonating at 7.61 ppm is assigned as H3. At this stage, all protons are assigned with no contradiction and this means that the structure of **5**, especially the site of bromine, is unequivical.

Assignment of **6**.

The proton nmr of **6** characteristically shows four downfield doublets at 8.78 ppm, 8.89 ppm, 8.92 ppm, and 9.13 ppm. Considering the structure of **6**, these four signals could be easily assigned as bay-region protons (H5, H6,
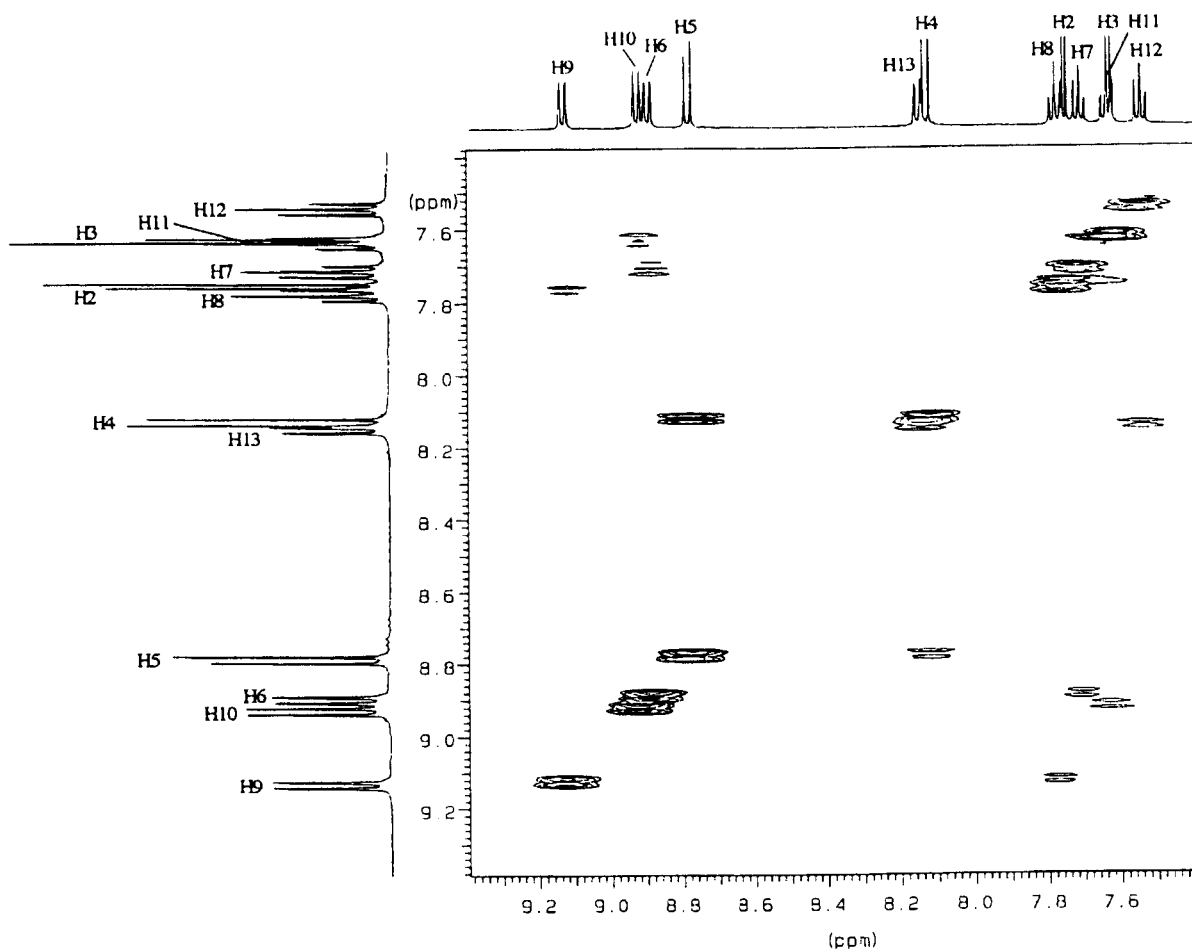

Figure 2. ^{1}H-^{1}H pfg-COSY Spectrum of **6**.

H9, and H10). Furthermore, among these four signals, the ^{1}H-^{1}H pfg-COSY spectrum (Figure 2) shows that 1) the signal resonating at 8.78 ppm is included in the two-spin system; 2) both signals resonating at 8.89 ppm and 9.13 ppm are included in the same four-spin system; 3) the signal at 8.92 ppm is included in another four-spin system. These facts establish that the signal at 8.78 ppm which was a counterpart of the two-spin system and besides a bay-region proton, was assigned as H5. Between two four-spin systems, the system which contains H10-13 has only one bay-region proton (H10), and the other four-spin system containing H6-9 has two bay-region protons (H6 and H9). Therefore, the signal at 8.92 ppm which is the only proton in bay-region among the components of a four-spin system, was assigned as H10. The signals resonating at 8.89 ppm and 9.13 ppm are H6 and H9, however, we could not distinguish which proton was which position at this stage. Both H5 and H10 are good starting points for the identification of these protons. As described above, H5 is a signal which is included in a two-spin system. Therefore, the

counterpart of this two-spin system is assigned as H4 and this is observed at 8.12 ppm as a one proton doublet (J = 8.5 Hz). In the NOESY spectrum of **6** (Figure 3) a correlation was found between H5 (8.75 ppm) and a signal at 8.89 ppm and not between H5 and a signal at 9.13 ppm. So that, the signal resonating at 8.89 ppm is assigned as H6, meanwhile, the signal at 9.13 ppm is assigned as H9. In the ^{1}H-^{1}H pfg-COSY spectrum, the remaining two protons, H7 and H8, in the four-spin system including H6 and H9 are easily assigned by tracing the correlations in this four-spin system, that is, the signal at 7.71 ppm is assigned as H7 and the signal at 7.77 ppm is H8. With regard to the other four-spin system including H10, it was accomplished in a similar manner by starting from H10 and tracing the correlations which gave the assignments of H11 (7.63 ppm), H12 (7.53 ppm), and H13 (8.14 ppm). The observation of the correlation between H9 and H10 in the NOESY spectrum also consfirmed these assignments. Finally the remaining protons (H2 and H3) correspond to an AB quartet (J = 5.5 Hz) at 7.62 ppm and 7.75 ppm. Usually H2 of
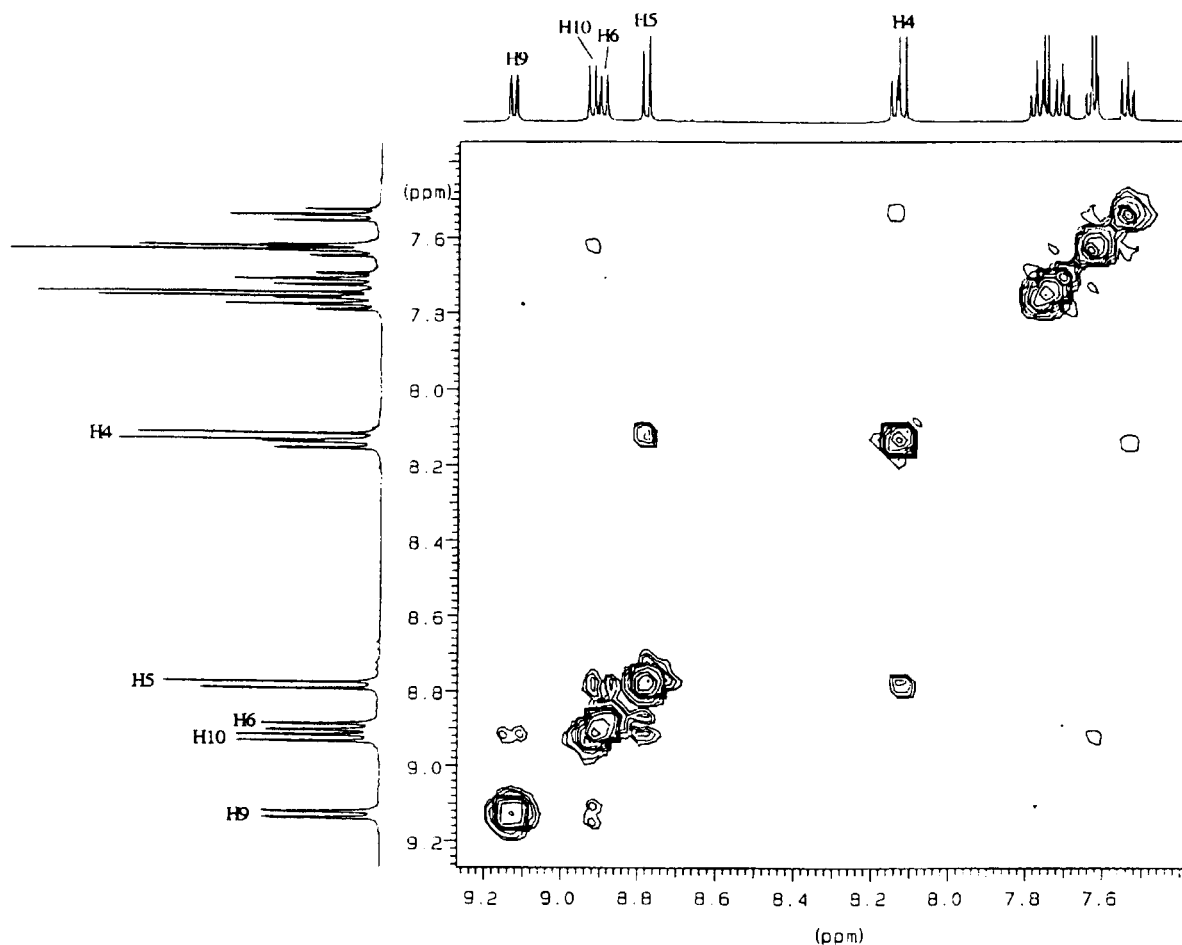

Figure 3. NOSEY Spectrum of **6**.

benzo[*b*]thiophene is observed at 7.40 ppm (J = 6 Hz) and it is shifted 0.11 ppm lower than that of H3 [7]. This relationship between H2 and H3 of benzo[*b*]thiophene can be applied to **6**, because there is no factor to change this relationship in **6**. This means that the lower signal resonating at 7.75 ppm is assigned as H2 and the higher signal at 7.62 ppm is H3. In the HMQC using a pulsed field gradient probe (pfg-HMQC) spectrum of **6** (Figure 4), the ^{1}H signal at 7.75 ppm (H2) has a correlation with the lower ^{13}C signal at 127.1 ppm and the ^{1}H signal at 7.62 ppm (H3) has that with the higher ^{13}C signal at 124.4 ppm and these facts established the assignments of H2 and H3 described above. At this point one can complete the assignment of the ^{1}H nmr spectrum using the data from the ^{1}H-^{1}H pfg-COSY and NOESY spectra.

As shown in Figure 4, all protonated carbons were easily assigned using the pfg-HMQC spectrum.

For the assignment of the quaternary carbons, we shall start from the quaternary carbon which has the lowest resonance at 139.9 ppm in the HMBC using a pulsed field gradient probe (pfg-HMBC) spectrum of **6** shown in Figure 5. This carbon has correlations with H10 and H12. So that, it can be assigned as C13a. The carbon resonating at 136.6 ppm is assigned as C9c on the basis of both correlation with H11 and H13. The carbon resonating at 136.1 ppm which correlated with H2, H3, and H4 can be assigned as C14c. There are two quaternary carbons resonating at 129.9 ppm and 128.4 ppm, both of which have correlations with

H9. Between these signals, only the signal at 129.9 ppm correlates with H5 and H7, while on the other hand, the signal at 128.4 ppm has no correlation except for that with H9. Therefore, the quaternary carbon at 129.9 ppm can be assigned to C5b, and the other quaternary carbon to C9b. Similarly, between the signals resonating at 129.4 ppm and 127.6 ppm, both of which have correlations with H6, the signal at 129.4 ppm also correlated with H8 and the other at 127.6 ppm was correlated with H4. Therefore, the signal at 129.4 ppm was assigned to C9a and the other at 127.6 ppm to C5a. The signal at 123.9 ppm, which is resonating at the highest field among the quaternary carbons, was assigned as C3a because of its correlations with H2 and H5. At this point, the remaining quaternary carbons are C14a and C14b. With regard to the remaining two signals resonating at 139.0 ppm and 135.9 ppm, the signal at 139.0 ppm has correlations with H2, H3, and H5, while on the other hand, the signal at 135.9 ppm has no correlation with any protons. Considering the structure of **6**, the distance between C14b and H2, and C14b and H3 are both four bonds, not three bonds. However, there are zigzag relationships between C14b and H2, and C14b and H3, therefore it is reasonable that correlations be found between them. On the basis of what is described above, the signal at 139.0 ppm can be assigned as C14b and the signal at 135.9 ppm as C14a. No correlation was found between C5 and any protons except for the one bond coupling (C5-H5). Proton and ^{13}C chemical shifts of **6** are listed in Table 1.
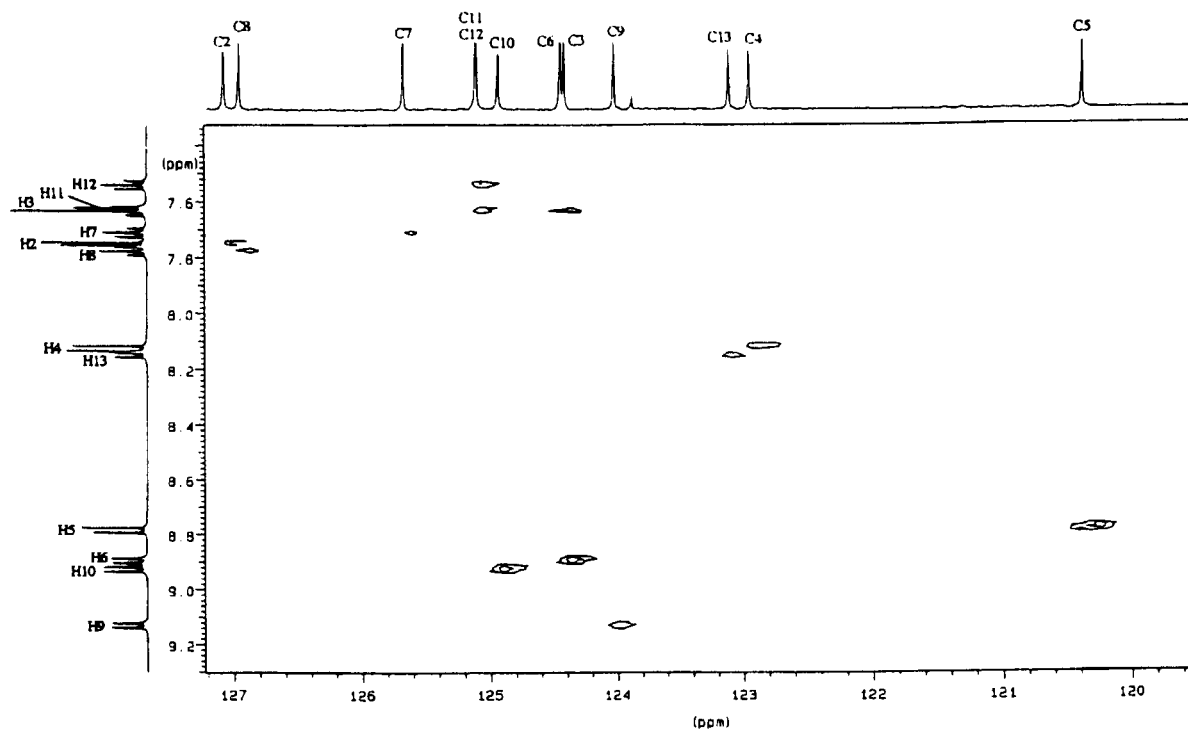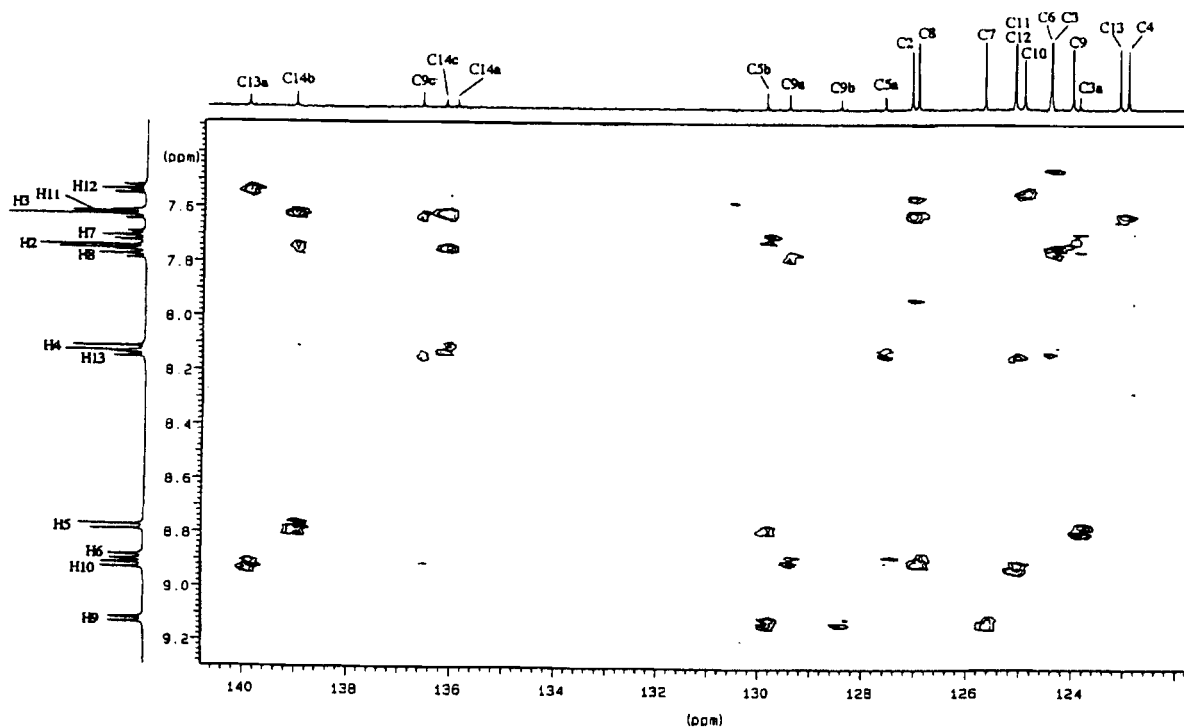

Figure 4. pfg-HMQC Spectrum of **6**.

Figure 5.   pfg-HMBC Spectrum of **6**

Table 1

^{1}H and ^{13}C Chemical Shifts, Coupling Pattern,
Coupling Constants (Hz), and Long Range Correlation of
Naphtho[2,1-*b*:4,3-*g*]bisbenzo[*b*]thiophene (**6**)

Position	δH	δC	Long Range Correlation
2	7.75, d (J = 5.5)	127.1	H3
3	7.62, d (J = 5.5)	124.4	H2, H4
3a		123.9	H2, H5
4	8.12, d (J = 8.5)	122.9	H3
5	8.78, d (J = 8.5)	120.4	none
5a		127.6	H4, H6
5b		129.9	H5, H7, H9
6	8.89, d (J = 8.2)	124.4	H8
7	7.71, t (J = 8.2)	125.7	H9
8	7.77, t (J = 8.2)	127.0	H6
9	9.13, d (J = 8.2)	124.0	H7
9a		129.4	H6, H8
9b		128.4	H9
9c		136.6	H10, H11, H13
10	8.92, d (J = 8.2)	124.9	H12
11	7.63, t (J = 8.2)	125.1	H13
12	7.53, t (J = 8.2)	125.1	H10
13	8.14, d (J = 8.2)	123.1	H11
13a		139.9	H10, H12
14a		135.9	none
14b		139.0	H2, H3, H5
14c		136.1	H2, H3, H4

In conclusion, we have synthesized the novel hetero-cyclic ring system naphtho[2,1-*b*:4,3-*g*]bisbenzo[*b*]thio-phene (**6**). The complete assignments of the ^{1}H and ^{13}C spectra of **6** has been accomplished by concerted usage of pfg-COSY, NOESY, pfg-HMQC, and pfg-HMBC two-dimensional nmr techniques.

EXPERIMENTAL

All melting points were determined on a Yanagimoto micro-melting point apparatus, and are uncorrected. The ir spectra were recorded on a Japan Spectroscopic IRA-102 diffraction grating infrared spectrophotometer and frequencies are expressed in cm^{-1}. The ^{1}H and ^{13}C nmr spectra were acquired on a Varian VXR-500 instrument working at 500 MHz operating at an observation fre-quency of 499.01 MHz for ^{1}H and 125.69 MHz for ^{13}C in the sol-vent indicated with tetramethylsilane as the internal standard. All experiments were taken at 45°. Chemical shifts are given in ppm (δ) and J values in Hz, and the signals are designated as follow; s, singlet; d, doublet; t, triplet; m, multiplet. The ^{1}H-^{1}H COSY, HMQC, and HMBC experiments were performed using a pulsed field gradient probe and the NOESY experiment was performed using an indirect probe (proton 90° pulse = 14.5, carbon 90° pulse = 16.5). The HMQC experiment was performed using the Varian pulse program optimized for direct coupling (140 Hz, $^1J_{CH}$). The HMBC experiment was performed using the Varian pulse program optimized for 8 Hz $^3J_{CH}$ coupling. The EI-mass and high resolution EI-mass spectra were measured on a VG 70 mass spectrometer. Elemental analyses were performed on a Yanagimoto MT-5 CHN Corridor elemental analyzer.

2-Bromo-3-bromomethylthiophene (**2**).

To a solution of 3-methylthiophene (**1**, 9.0 g, 92 mmoles) and benzoyl peroxide (0.1 g, 0.41 mmole) in dry benzene (500 ml) was gradually added a mixture of N-bromosuccinimide (20 g,

112 mmoles) and benzoyl peroxide (0.1 g, 0.41 mmole) under reflux during 1 hour; the reaction mixture was refluxed for 1 additional hour. After cooling the reaction mixture, the precipitate was filtered off and the filtrate was evaporated *in vacuo*. The orange oily residue (15.6 g) was used in the next step without further purification because of its instability.

Diethyl (2-Bromo-3-thenyl)phosphonate (3).

A solution of the oily residue obtained above (2, 15.6 g) in triethyl phosphite (15 ml, 88 mmoles) was refluxed for 5 hours. After removal of the unreacted triethyl phosphite at 50-70°/20 mm Hg, the residue (12 g) was used for the next step without further purification because of its instability.

5-[2-(2-Bromo-3-thienyl)ethenyl]naphtho[2,1-*b*][1]benzothiophene (5).

To a solution of 4 (0.7 g, 2.7 mmoles) and the above residue (6.0 g) in dry 1,2-dimethoxyethane (40 ml) was added 60% sodium hydride (0.16 g, 6.7 mmoles), and the mixture was stirred at room temperature for 3 hours. After stirring, the reaction mixture was poured into ice-water (*ca.* 200 g), and the mixture was extracted with diethyl ether. The organic layer was washed with water, dried over anhydrous sodium sulfate, and evaporated to dryness. The residue obtained was chromatographed on silica gel. The elution with *n*-hexane-benzene (1:1, v/v) was evaporated and recrystallized from ethyl acetate to give 200 mg (18%, overall yield from 1) of 5 as yellow prisms, mp 182-185°; ^1H nmr (deuteriochloroform): δ 7.20 and 7.80 (each d, J = 16, each 1H, Hα and Hβ), 7.31 (d, $J_{4',5'}$ = 5.8, 1H, H4'), 7.35 (d, $J_{5',4'}$ = 5.8, 1H, H5'), 7.48, 7.56, 7.61 and 7.74 (each t, J = 8.3, each 1H, H2, H3, H9 and H10), 7.98, 8.31, 8.81 and 9.02 (each d, J = 8.3, each 1H, H1, H4, H8 and H11), 8.14 (s, 1H, H6); ms: EI m/z 422 (M$^+$ + 2, 30%), 420 (M$^+$, 30%), 341 (M$^+$ - Br, 100%).

Anal. Calcd. for $C_{22}H_{13}BrS_2$: C, 62.71; H, 3.11. Found: C, 62.60; H, 3.27.

Naphtho[2,1-*b*:4,3-*g*]bisbenzo[*b*]thiophene (6).

A solution of 5 (50 mg, 0.12 mmole) in benzene (500 ml) containing triethylamine (*ca.* 0.05 ml) was irradiated for one hour with a 500 watt high pressure mercury lamp. The solvent was evaporated *in vacuo* and the residue was chromatographed on silica gel. Elution with *n*-hexane-chloroform (9:1, v/v) provided the eluate which was evaporated and the residue was recrystallized from acetone to give 14 mg (34%) of 6 as colorless needles, mp 201-202°; ms: EI m/z 340 (M$^+$, 100%); hrms: EI m/z Calcd. for $C_{22}H_{12}S_2$: 340.0380. Found: 340.0393.

REFERENCES AND NOTES

[1]　　Part 1: K. Sasaki, O. Tokuda, T. Hirota, J.-K. Luo, and R. N. Castle, *J. Heterocyclic Chem.*, **32**, 1735 (1995).

[2]　　To whom correspondence should be directed at the Faculty of Pharmaceutical Sciences, Okayama University, Tsushima, Okayama 700, Japan (Kenji Sasaki) or the Department of Chemistry, University of South Florida, Tampa, FL 33620-5250, USA (Raymond N. Castle).

[3]　　J.-K. Luo, R. F. Federspiel, and R. N. Castle, *J. Heterocyclic Chem.*, **32**, 659 (1995), and references cited therein.

[4a]　　H. Kudo, M. L. Tedjamulia, R. N. Castle, and M. L. Lee, *J. Heterocyclic Chem.*, **21**, 185 (1984); [b] M. L. Tedjamulia, H. Kudo, R. N. Castle, and M. L. Lee, *J. Heterocyclic Chem.*, **21**, 321 (1984).

[5]　　W. J. Archer, R. Cook, and R. Taylor, *J. Chem. Soc., Perkin Trans. II*, 813 (1983).

[6]　　J. Guillaume, L. Nédélec, M. Cariou, and A. Allais, *Heterocycles*, **15**, 1227 (1981).

[7]　　E. Pretsch, T. Clerc, J. Seibl, and W. Simon, in Table of Spectral Data for Structure Determination of Organic Compounds, W. Fresenius, J. F. Huber, E. Pungor, G. A. Rechnitz, W. Simon, and T. S. West, eds, Springer-Verlag, Berlin, 1989, p H265, H325.