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The Improved Synthesis, Diels-Alder Reactions, and Desulfuration of Trithio-1,8-naphthalic Anhydride

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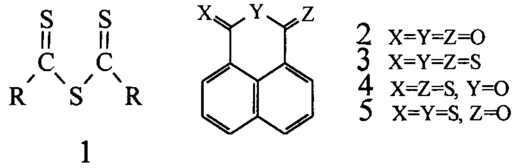
ABSTRACT: *In the presence of a strong Lewis base, such as* Et_3N*, trithio-1,8-naphthalic anhydride (***3***) is easily oxidized. Two improved syntheses of trithio-1,8-naphthalic anhydride (***3***) are described. Trithio-1,8-naphthalic anhydride (***3***) undergoes Diels-Alder reactions with electron-deficient alkenes to give novel fused heterocyclic compounds (***6–11***) that then can undergo a novel, gradual desulfuration dimerization with triethyl phosphite to afford* **12** *and its analogs* **13** *and* **14***. The structures of* **6–14** *are confirmed by microanalysis, IR, and NMR spectroscopy, and MS.* © 1999 John Wiley & Sons, Inc. Heteroatom Chem 10: 141–146, 1999

INTRODUCTION

Although the chemistry of thione analogues, such as ketones, acids, esters, and amides, is well developed [1], and the literature on radical reactions associated with thiones is extensive [2,3], little is known concerning the chemistry of thioanhydrides. Kato [4] found that aliphatic thioanhydrides (**1**, R = aliphatic, see Scheme 1) are highly unstable, whereas aromatic ones (**1**, R = aromatic) are fairly stable. Cava [5–7] reported the first cyclic trithioanhydride, trithio-1,8-naphthalic anhydride (**3**, see Scheme 1) synthesized in 13.6% yield by the sulfuration of 1,8-naphthalic anhydride (**2**, see Scheme 1) with Lawesson's reagent (**LR**, 2,4-bis(*p*-methoxylphenyl)-1,3,2,4-dithiadiphosphetane-2,4-disulfide), and he found that **3** is very stable.



SCHEME 1

Furthermore, hetero-Diels-Alder reactions have become a powerful tool for the construction of heterocyclic rings [8,9]. [4 + 2] Cycloaddition of enethiones [7] or ortho-bisthiones [10] with electron-rich alkenes and [2 + 4] cycloaddition of thiones [11] with 1,3-dienes have been observed.

These prompted us to explore the sulfuration of 1,8-naphthalic anhydride with appropriate phosphorus reagents in the hope of raising the yield of trithio-1,8-naphthalic anhydride (**3**) and to further investigate its chemical properties. We now report two one-pot procedures to synthesize **3** in 70% and 66% yields. We also report Diels-Alder reactions of **3** with electron-deficient alkenes to give fused heterocyclic products (**6–11**), and the desulfuration dimerization of trithio-1,8-naphthalic anhydride (**3**) with triethyl phosphite to give **12–14**.

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RESULTS AND DISCUSSION

Sulfuration of 1,8-Naphthalic Anhydride with Phosphorus Reagents: Improved Synthesis of 3

Cava's sulfuration route [5,7] for the preparation of trithio-1,8-naphthalic anhydride (**3**) involved three steps with a total yield of 13.6%: (1) dithionation of 1,8-naphthalic anhydride **2** with **LR** furnished dithiono-1,8-naphthalic anhydride **4**, (2) **4** was rearranged by the action of catalytic amount of Et_3N to thiolothiono-1,8-naphthalic anhydride **5**, and (3) thionation of **5** gave the product **3** (see Scheme 2).

We have found two efficient one-pot procedures to obtain **3** in 76% and 66% yields. They are shown in Schemes 3 and 4.

One is a modified procedure based on Cava's method. In an early attempt, in order to realize the trisulfuration of naphthalic anhydride (**2**) in one step, we used excess **LR** and some solvents with relatively higher boiling points such as xylene, dichlorobenzene, or trichlorobenzene, instead of chlorobenzene, but only the dithionation product **4** was obtained in a relatively low yield. This was ascribed to inertness of the ether-type oxygen and to partial decomposition of LR above 140°C [12]. Barton's work [13] on naphthiazine-4-thione led us to test other sulfuration reagents, such as P_4S_{10}/Py, LR/Py, LR/DBU, LR/Et_3N. Unexpectedly, these systems did not give any thionation product from **2** at all. Both **LR** and pure **3** easily decompose in the presence of the indicated Lewis bases. Monitoring of the reaction mixture by silica gel TLC, using light petroleum ether-ethyl acetate (4:1) as eluent, indicated the complete disappearance of 1.2 g of **3** during 1.5 hours in the presence of 5 drops of Et_3N in 20 mL of boiling chlorobenzene and showed the complete decomposition of 2 g of **LR** in a half hour in the presence of 5 drops of Et_3N in 20 mL of boiling chlorobenzene. In view of these facts, we designed a new procedure as depicted in Scheme 3, in which the catalyst Et_3N was removed before the third sulfuration. The operations included a direct bis-thionation of **2** affording **4**; addition of a catalytic amount of Et_3N; and, after the rearrangement of **4** to **5**, evaporation of the catalyst Et_3N and then in situ a third thionation of **5** with a half equivalent of **LR** to form **3**, in a total 76% yield.

$$2 \xrightarrow[\text{PhCl}]{\text{LR}} 4 \xrightarrow[\text{cat.}]{Et_3N} 5 \xrightarrow[\text{PhCl}]{\text{LR}} 3$$

SCHEME 2

$$2 \xrightarrow[76\%]{\text{①LR/PhCl, ②}Et_3N\text{(cat.), ③LR/PhCl}} 3$$

SCHEME 3

$$2 \xrightarrow[66\%]{\text{LR, PhCl; }PhNMe_2\text{/Cat..}} 3$$

SCHEME 4

Another successful synthesis is outlined in Scheme 4. Compound **2** was reacted with **LR** in the presence of a catalytic amount of $PhNMe_2$ with a stepwise style addition of **LR** and $PhNMe_2$. The product **3** was obtained in a yield of 66%. Monitoring by TLC showed us that the base $PhNMe_2$ only partially decomposed **LR** and **3** in PhCl under reflux during 2 hours.

Diels-Alder Reaction of 3 *with Electron-Deficient Alkenes*

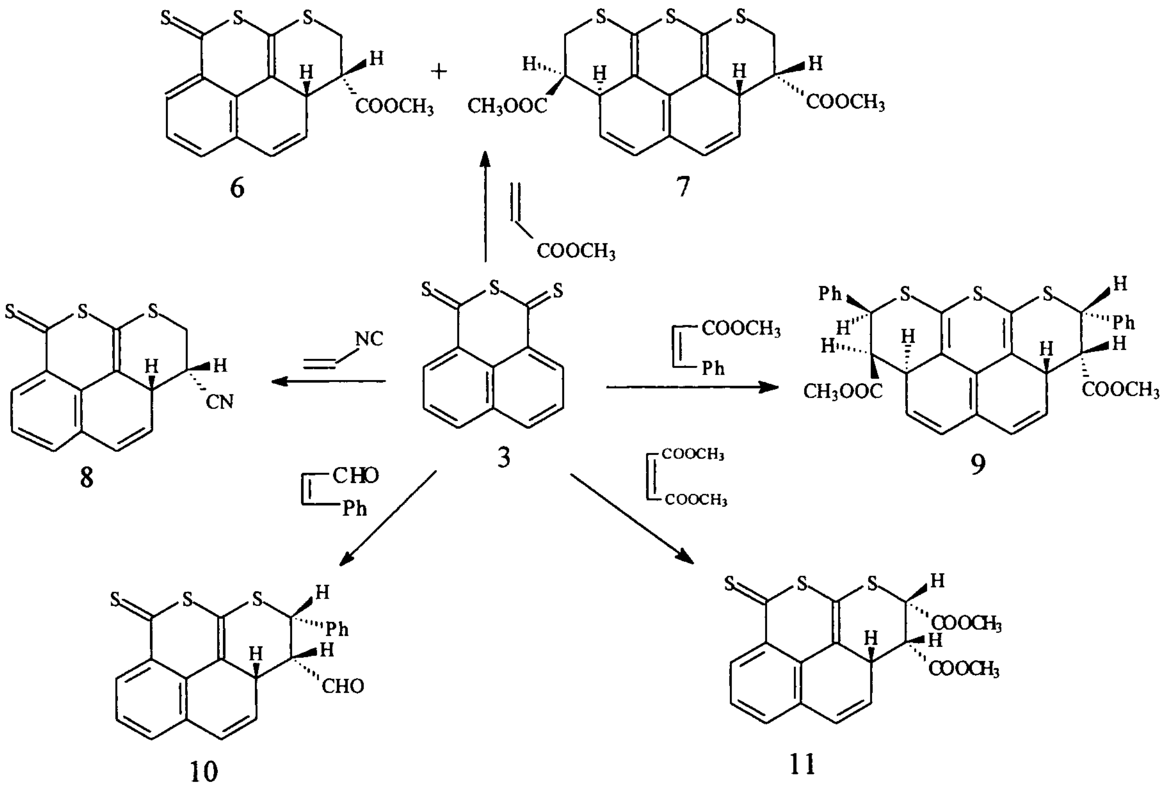
Cava showed an inverse demand [2 + 4] cycloaddition of electron-rich alkenes to **3** [5,7]. Here, we found that the electron-deficient alkenes can also function as ene-partners in Diels-Alder reactions with the ene-thione moiety of **3**, albeit slowly (see Scheme 5).

Cycloaddition was observed when **3** was heated with any of the electron-deficient alkenes shown in Scheme 5 but not with maleic anhydride. Maleic anhydride is probably too electron deficient to react with **3**. The resulting colored products were shown to have structures **6–11** by ^1H NMR and FTIR spectroscopy, MS, and microanalyses. The data are listed in the Experimental section. The yields are good (31–89%). As to the configurations, those depicted in Scheme 5 are tentative; they were assigned on the basis of the theoretical *endo principle* [16]. The regioselectivity of addition was crucially examined by ^1H NMR spectroscopy and consideration of the cationic fragments in MS for **6–11**. For example, the dd-type peaks at $\delta = 4.50$ and 4.52 in the ^1H NMR spectra of **9** and **10** were assigned to the -(Ph)CHC*H*(COR)CH< linkage, not to the -(RCO)CHC*H*(Ph)CH< structure. Two peaks at *m/z* 121 in the MS of **9** and **10** indicate that both molecules include the Ph-C-S group. The bis-addition products of **7** and **9** are a mixture of the C_2 isomer (shown in Scheme 5) and the C_S isomer (not shown in Scheme 5), the structures of which are supported by their ^1H NMR spectra. For example, the ^1H NMR spectra of **7** and **9** give two kinds of MeO group resonance signals. All of these results indicate that the ene-thione moiety of the aromatic thioanhydride is electron deficient in Diels-Alder reactions. This is an extension of Cava's conclusion [5,7].

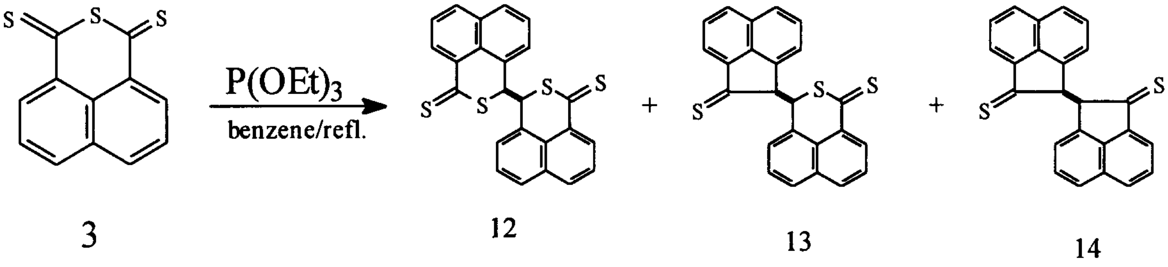
Desulfuration of Trithio-1,8-naphthalic Anhydride (3) with P(OEt)$_3$

Compound **3** was found to undergo a novel, gradual desulfuration dimerization to furnish both **12** and analogues **13** and **14** in refluxing benzene under a dry nitrogen atmosphere with P(OEt)$_3$ (see Scheme 6) but not with Ph$_3$P. The three colored products were purified by preparative TLC on silica gel with petroleum ether-AcOEt as eluent, and characterized by MS, FTIR, and ^{1}H NMR spectroscopy and microanalyses. Desulfuration of **3** in refluxing CH$_2$Cl$_2$ (40°C) occurred very slowly; whereas in refluxing P(OEt)$_3$ (150°C), no **12**, but only **13** and **14** were obtained. In refluxing CHCl$_3$ for one week, the reaction gave only red **12**. Compound **12** was sensitive to air at room temperature. The values of R_f of **13** and **14** were close to each other, and both were smaller than that of **12**.

On the basis that deoxygenation dimerization of the anhydride requires a higher temperature [14], the desulfuration dimerization of the thioanhydride might be viewed as an alternative route to that operation in the synthesis of the dimer of anhydrides.



SCHEME 5



SCHEME 6

EXPERIMENTAL

Spectroscopic Measurements. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 300 MHz and 75 MHz on a Brucker AM 300 MHz spectrometer and were referenced to internal Me_4Si (0.00 ppm). Electrospray ionization mass spectral (ESI-MS) data were obtained on a VG-QUATTRO spectrometer with an H_2O-CH_3OH solution. Electron ionization mass spectral (EI-MS) data were recorded on a Hewlett-Packard HP5988A spectrometer at 70 ev. FT-IR was recorded on a Nicolet 5SXC spectrometer.

Reagents. The 2,4-bis(*p*-methoxylphenyl)-1,3,2,4-dithiadiphosphetane-2,4-disulfide (Lawesson's reagent, **LR**) [15] was prepared according to the reported procedures. Triethyl phosphite and DBU were purchased from Fluka and Aldrich. Other reagents were obtained commercially and distilled before use. All reactions were conducted under an atmosphere of oxygen-free nitrogen using Schlenk line techniques.

Synthesis of Trithio-1,8-naphthalic Anhydride (*3*). Method A: To a boiling solution of 1,8-naphthalic anhydride **2** (19.80 g) in chlorobenzene (750 mL) was added Lawesson's reagent (40.40 g) in portions, in the course of 3 hours. The mixture was refluxed for 12 hours. A brick red solid appeared. After the mixture had been cooled to 50°C, 5 mL of triethylamine was added. The mixture was stirred at 60°C for 4 hours. The red suspension turned into a dark green solution. Following evaporation of all of the triethylamine and 150 mL of chlorobenzene, a boiling dark green solution resulted, and to this was added the Lawesson's reagent (20.20 g) in portions, within 1 hour. The mixture was refluxed for 2 hours. About 300–350 mL of chlorobenzene was distilled off under reduced pressure. The residue was heated with 200 mL of ethanol for 0.5 hour, and the resulting dark red solid was filtered off, dried, and recrystallized from chlorobenzene to afford 19.0 g (76%) of pure trithio-1,8-naphthalic anhydride (**3**). Method B: To a boiling solution of 1,8-naphthalic anhydride **2** (4 g) in chlorobenzene (50 mL) was added stepwise Lawesson's reagent (4.20 g × 3) and N,N-dimethylaniline (1 mL × 2) in four portions, in the course of 9 hours. After the mixture had been refluxed for another 2 hours, 30 mL of chlorobenzene was distilled off under reduced pressure. The residue was heated with 10 mL of ethanol, and the resulting dark red solid was filtered off, dried (4.20 g), and further recrystallized from chlorobenzene to afford 3.60 g (66%) of pure trithio-1,8-naphthalic anhydride (**3**): mp 222–223 (dec.) (225°C);[7] IR (cm^{-1}) 1542, 1500, 1255 (C = S), 1172, 1110, 1040, 960, 880, 810.

Diels-Alder Reactions: Adducts **6** *and* **7** *from* **3** *and Methyl Acrylate.* The mixture of trithio-1,8-naphthalic anhydride (**3**, 0.246 g, 1 mmol) and methyl acrylate (5 mL) was refluxed at 80°C for 6 hours. The excess methyl acrylate was evaporated, and the residue was chromatographed on silica gel by preparative TLC using light petroleum ether/ethyl acetate (4/1) as eluent to give the brown yellow adduct **6** and adduct **7**. Adduct **6** (110 mg, 33%) mp 236–238°C; NMR δ: 8.60 (d, 1H, 7.2 Hz), 7.70 (m, 2H), 7.05 (m, 1H), 6.75 (m, 1H), 4.35 (m, 1H), 3.74 (s, 3H), 3.55 (m, 1H), 2.95 (br, 2H); ESI-MS (m/e, %): 333(M + 1, 99%), 301(M + 1-S, 60%), 294 (M + 1-C_3H_3, 100%), 252 (27%), 247 (M + 1-$C_4H_6O_2$, 45%), 219 (92%), 148 ($C_{12}H_4$,43%), 102 (33%); IR (cm^{-1}): 1723 (C = O), 1260 (C = S); anal. calcd for $C_{16}H_{12}O_2S_3$: C, 57.83; H, 3.61. Found: C, 57.69; H, 3.65. Adduct **7** (213 mg, 51%): mp 101–102°C; NMR δ: 6.77 (m, 1H), 6.65 (m, 1H), 6.50 (m, 1H), 6.41 (m, 1H), 4.30 (m, 2H), 3.85 (s, 3H), 3.70 (s, 3H), 3.55 (m, 2H), 2.95 (br, 4H); ESI-MS (m/e,%): 332 (M-$C_4H_6O_2$, 13%), 301 (27%), 264 (10%), 219 (100%), 203 (8%), 149 (17%); IR cm^{-1} 2920, 2850, 1738 (C = O), 1640, 1170, 1010, 840; anal. calcd. for $C_{20}H_{18}O_4S_3$: C, 57.42; H, 4.31. Found: C, 57.40; H, 4.34.

Adduct **8** *from* **3** *and Acrylonitrile.* The mixture of trithio-1,8-naphthalic anhydride (**3**, 0.246 g, 1 mmol) and acrylonitrile (5 mL) was refluxed at 78°C for 12 hours. The excess acrylonitrile was evaporated, and the residue was chromatographed on silica gel by preparative TLC using light petroleum ether/ethyl acetate (5/1) as eluent to give the adduct **8** (178 mg, 59.7%): mp 198–200°C; NMR δ: 8.68 (m, 1H), 7.77 (m, 2H), 6.95 (m, 1H), 6.55 (m, 1H), 5.00 (m, 1H), 3.60 (m, 1H), 2.90 (m, 1H), 2.70 (m, 1H); ESI-MS(m/e, %): 300 (M + 1, 100%), 219 (42%), 149 (13%), 119 (16%), 91 (15%), 63 (10%); IR cm^{-1}: 2250 (C ≡ N), 1560, 1420, 1300, 1230 (C = S), 1010, 830, 770; anal. calcd for $C_{15}H_9NS_3$: C, 60.20; H, 3.01. Found: C, 60.15; H, 2.97.

Adduct **9** *from* **3** *and Methyl Cinnamate.* The mixture of trithio-1,8-naphthalic anhydride (**3**, 0.246 g, 1 mmol) and methyl cinnamate (5 mL) was refluxed at 180°C for 4 hours. The excess methyl cinnamate was evaporated under reduced pressure, and the residue was chromatographed on silica gel by preparative TLC using light petroleum ether/ethyl acetate (4/1) as eluent to give adduct **9** (274 mg, 89.0%): mp 88°C; NMR δ: 7.30 (m, 10H), 6.75 (m, 2H), 6.45 (m, 2H), 4.70 (m, 2H), 4.50 (dd, 7.2 Hz, 7.1 Hz, 2H), 3.60 (m, 2H), 3.45 (s, 3H, MeO), 3.40 (s, 3H, MeO); ESI-MS (m/e, %): 527 (M-CS, 25%), 511 (M-COOMe, 50%), 421 (41%), 381 (90%), 219 (50%), 133

(100%), 121 (PhCS, 14%); IR (cm^{-1}) 2940, 2850, 1730 (br), 1460, 1380, 1210, 765, 690; anal. calcd for $C_{32}H_{26}O_4S_3$: C, 67.36; H, 4.56. Found: C, 67.42; H, 4.51.

Adduct **10** *from* **3** *and Cinnamaldehyde.* The mixture of trithio-1,8-naphthalic anhydride (**3**, 0.246 g, 1 mmol) and methyl cinnamate (278 mg) in toluene (5 mL) was refluxed for 4 hours. The solvent was evaporated under reduced pressure, and the residue was chromatographed on silica gel by preparative TLC using light petroleum ether/ethyl acetate (4/1) as eluent to give adduct **10** (292 mg, 77.3%): mp 142–144°C; NMR δ 10.55 (d, 7.7 Hz, 1H), 8.80 (d, 7.27 Hz, 1H), 7.80–6.70 (m, 8H), 6.40 (m, 1H), 4.75 (d, 7.7 Hz, 1H), 4.52 (dd, 7.25 Hz, 6.99 Hz, 1H), 3.75 (m, 1H); EI-MS (m/e, %): 378 (M$^+$, 3%), 346 (M-S, 100%), 314 (M-2S, 21.6%), 246 (M-PhCH$=$CHCHO, 31.86%), 239 (20%), 132 (PhC_2H_2CHO, 6.78%), 121 (PhCS, 14.22%), 91 (38%); IR (cm^{-1}): 1720, 1240. Anal. calcd for $C_{21}H_{14}OS_3$: C, 66.67; H, 3.70. Found: C, 66.65; H, 3.71.

Adduct **11** *from* **3** *and Dimethyl Maleate.* The mixture of trithio-1,8-naphthalic anhydride (**3**, 0.246 g, 1 mmol) and dimethyl maleate (5 mL) was heated at 100°C for 4 hours. The dimethyl fumarate that had isomerized from dimethyl maleate was evaporated under reduced pressure, and the residue was chromatographed on silica gel by preparative TLC using light petroleum ether/ethyl acetate (2/1) as eluent to give the red adduct **11** (121 mg, 31%): mp 100–101°C; NMR δ: 8.40 (d, 7.55 Hz, 1H), 8.15 (t, 7.2 Hz, 1H), 7.65 (m, 1H), 6.80 (m, 1H), 6.65 (m, 1H), 5.80 (d, 7.1 Hz, 1H), 4.75 (m, 1H), 3.90 (m, 1H), 3.77 (s, 3H), 3.73 (s, 3H); ESI-MS (m/e, %): 390 (M$^+$, 8%), 301 (11%), 280 (100%), 238 (50%), 219 (24%), 196 (14%), 148 (25%), 106 (20%), 64 (27%); IR (cm^{-1}): 1735 (C$=$0), 1240 (C$=$S). Anal. calcd for $C_{18}H_{14}O_4S_3$: C, 55.39; H, 3.59. Found: C, 55.36; H, 3.62.

Desulfuration of Trithio-1,8-naphthalic Anhydride (**3**) *with Triethyl Phosphite:* **12**, **13**, *and* **14**. The mixture of trithio-1,8-naphthalic anhydride (**3**, 0.246 g, 1 mmol) and triethyl phosphite (354 mg, 3.0 mmol) in benzene (5 mL) was refluxed for 4 hours. The solvent was evaporated under reduced pressure, and the residue was chromatographed on silica gel by preparative TLC using light petroleum ether/ethyl acetate (4/1) as eluent to give adducts **12**, **13**, and **14**. Adduct **12** (29.5 mg, 13.8%): red solid, mp 62°C; NMR δ 8.80 (dd, 7.5 HZ, 1.2 Hz, 2H), 8.40 (dd, 7.5 Hz, 1.2 Hz, 2H), 8.23 (dd, 7.5 HZ, 1.2 Hz, 2H), 8.10 (dd, 7.5 HZ, 1.2 Hz, 2H), 7.80 (t, 8.0 Hz, 2H), 7.77 (t, 8.0 Hz, 2H); MS (m/e, %): 428 (M$^+$, 2.45%), 396 (M-S, 12%), 364 (M-2S, 12%), 332 (M-3S, 15%), 246 (31%), 215 (52%), 202 (52%), 202 (18%), 170 (25%), 139 (13%), 126 (18%), 93 (32%), 85 (15%), 83 (16%), 81 (13%), 71 (20%), 69 (24%), 29 (100%), 27 (69%); IR (cm^{-1}): 1456, 1380, 1250, 1240, 1175, 1055, 950, 820, 780, 700, 600. Ana. calcd for $C_{24}H_{12}S_4$: C, 67.29; H, 2.80. Found: C, 67.35; H, 2.82. Adduct **13** (51.5 mg, 26.0%): orange oil, MS (m/e, %): 396 (M$^+$, 79.57%), 364 (M-S, 68.84%), 332 (M-2S, 82.98%), 244 (17%), 228 (100%), 215 (76.38%), 199 (64.46%), 1171 (72.69%); IR (cm^{-1}) 2975, 2910, 1450, 1390, 1260–1250, 1030, 970, 815, 800, 605, 580; anal. calcd for $C_{24}H_{12}S_3$: C, 72.73; H, 3.03. Found: C, 72.77; H, 3.05. Adduct **14** (64 mg, 35%): orange oil, MS (m/e, %): 364 (M$^+$, 39.97%), 332 (M-S, 43.21%), 300 (M-2S, 69.07%), 274 (44.13%), 211 (44.1%), 199 (25.32%), 178 (100%), 152 (24.14%); IR (cm^{-1}): 2980, 1480, 1450, 1420, 1390, 1250, 1010, 970, 820, 780, 590, 570; anal. calcd for $C_{24}H_{12}S_2$: C, 79.12; H, 3.30. Found: C, 79.23; H, 3.38.

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