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Synthesis of *S*-dialkylarsino-3-mercapto-1,2-propanediols and evaluation of their anticancer activity

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Abstract—Some new *S*-dialkylarsenic compounds, *S*-dialkylarsino-3-mercapto-1,2-propanediol (**3a**–**3d**) and their derivatives (**4a**,**4b**), have been synthesized. They were screened at the National Cancer Institute (NCI) for their anticancer activity against a panel of about 60 human tumor cell lines. Most of them display anticancer activity having GI_{50} and LC_{50} values at low concentrations and are sensitive to leukemia, renal cancer and prostate cancer cell lines and in which the compound **3c** is the most active.

1. Introduction

The use of arsenicals as therapeutic agents in medicine dates back more than 2400 years to ancient Greece and Rome.[1] In the 19th century, potassium arsenite, in the form of Fowler's solution, was used to treat a number of ailments.[2] During the past decade, arsenic compounds have become the subject of renewed attention. Since the mid 1990s inorganic arsenic oxides have been used in clinical trials and demonstrated to be efficient anticancer agents, especially for certain hemopoietic tumors. In September of 2000 the USA FDA approved the use of As_2O_3 for the treatment of relapsed or refractory acute promyelocytic leukemia (APL).[3] The mechanism associated with the beneficial anticancer effect of As_2O_3 is probably As_2O_3-induced apoptosis of the cancer cells.[3,4] Li, et al. [4c] have suggested that in myeloid cells, trivalent arsenic binds to two cysteine components in the globular structure of tubulin, blocks the binding site for GTP, and disrupts the normal dynamics of the microtubules during mitosis. This results in a genetic cascade that causes cell death and leads to apoptosis of the malignant cells. However, the toxicity associated with inorganic arsenic oxides presents a problem with respect to the use of inorganic arsenicals and limits their therapeutic application.[5] Takeshita has reported significant problems in controlling and maintaining stable heart rates during an APL treatment with As_2O_3.[6] The problem of serious toxicity common to virtually all inorganic arsenic compounds has led to a search for less toxic alternatives that display antitumor activity. Thus, organoarsenic compounds have received increased attention given to their relatively lower toxicity as compared with inorganic arsenicals.[7] For example, natural organoarsenic compounds have been discovered in seafood, mushrooms, lichens, and a variety of readily available plants, with arsenobetaine having been found to be essentially harmless.[7] Recently, Duzkale, et al. found that dimethylarsinic acid (DMAA) suppresses the cell colony grow of leukemia with no significant effect on the normal progenitor.[8] As a part of this search, we report arsenic derivatives that combine low toxicity with good anticancer activity.[9,10] We have synthesized a new organic arsenic derivative **3a** which combines the dimethylarsino group with 3-mercapto-1,2-propanediol. To further study the relationship between the structure and anticancer activity, the analogues **3b**–**d** and **4a**–**b** have also been synthesized.

2. Results and discussion

2.1. Chemistry

The preparation of compounds **3a**–**d** was straightforward. Thus, the reaction of **1** with dimethylchloroarsine or dialkyliodoarsine in chloroform in the presence of diethylamine yields the *S*-(dialkylarsino) derivatives (Scheme 1). This procedure was first reported by

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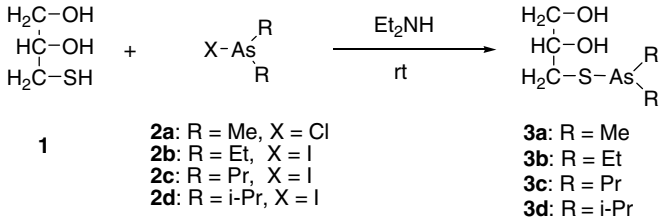
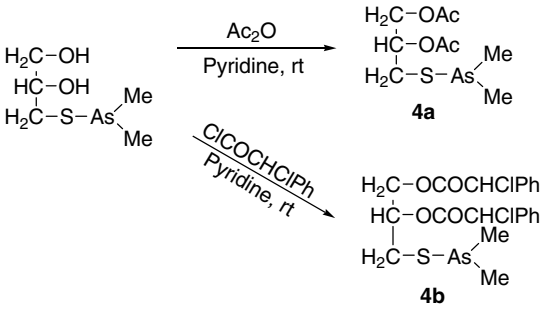


Scheme 1. Synthesis of compounds **3a**–**d**.



Scheme 2. Synthesis of compounds **4a**–**b**.

Zingaro.[11] It is to be noted that compound **3d** is not very stable and decomposes slowly at room temperature.

To a solution of **3a** and pyridine in dry chloroform (or dichloromethane) was added 2-chloro-2-phenylacetyl chloride or acetic anhydride. The mixture was stirred at room temperature. Then it was evaporated to remove solvent. The mixture was purified by flash column chromatography or evaporation under reduced pressure to get products (**4a**–**b**) in about 70–90% yield (Scheme 2).

2.2. Biology

The derivatives **3** and **4** were selected by the National Cancer Institute for testing against a panel of approximately 60 tumor cell lines. The in vitro test system and the information, encoded by the activity pattern over all cell lines, were obtained (see Section 4) according to reported methods.[12] The anticancer activity of a test compound is given by three parameters for each cell line; pGI_{50} value (GI_{50} is the molar concentration of the compound that inhibits 50% net cell growth), pTGI value (TGI is the molar concentration of the compound leading to total inhibition of net cell growth), and a pLC_{50} value (LC_{50} is the molar concentration of the compound that induces 50% net cell death). Moreover, a mean graph midpoint (MG-MID) is calculated for each of the mentioned parameters, giving an average activity parameter over all cell lines. For the calculation of the MG-MID, insensitive cell lines are included with the highest concentration tested. The selectivity of a compound with respect to a certain cell line of the screen is characterized by a high deviation of the particular cell line parameter compared to the MG-MID value.

An evaluation of the data reported in Table 1 reveals that dialkylarsino derivatives have high MG-MID values of pLC_{50} (4.34–5.52). Surprisingly, the di-*n*-propylarsino derivative, **3c**, is the most active in terms of pLC_{50} (mean value 5.52). Comparison of the data of the dialkylarsino-3-mercapto-1,2-propanediol series **3a**–**d** suggests that the substituents on the arsenic atom may play a significant role in the dialkylarsino-3-mercapto-1,2-propanediol series. The most active compound is the di-*n*-propyl derivative **3c** (pLC_{50} MG-MID = 5.52), followed by the diethyl derivative **3b** and the diisoproyl derivative **3d**, which showed similar pLC_{50} MG-MID values (4.91 and 4.85, respectively). The least active is the dimethyl derivative **3a** (mean value 4.34).

Table 1. Overview of the results of the in vitro antitumor screening for compounds **3** and **4**[a]

Compound	No. studied[e]	pGI_{50}[b]			pTGI[c]			pLC_{50}[d]		
		No. high sensitive results[e]	Range	MG-MID[f]	No. high sensitive results	Range	MG-MID	No. high sensitive results	Range	MG-MID
3a	53	28	4.87–6.74	5.88	27	4.00–6.24	4.99	16	4.00–5.41	4.34
3b	49	24	5.22–7.57	6.48	26	4.00–6.98	5.73	26	4.00–6.21	4.91
3c	46	18	5.64–8.00	6.78	26	4.00–7.56	6.31	21	4.00–6.83	5.52
3d	52	23	4.00–7.28	5.89	35	4.00–6.50	5.33	27	4.00–6.00	4.85
4a	49	23	5.45–8.00	6.71	21	4.00–7.22	5.87	23	4.00–6.18	4.91
4b	52	25	4.57–7.48	5.95	18	4.00–6.57	5.05	20	4.00–5.57	4.36

[a] Data obtained from the NCI's in vitro disease-oriented human tumor cell screen.
[b] pGI_{50} is the −log of the molar concentration that inhibits 50% net cell growth.
[c] pTGI is the −log of the molar concentration giving total growth inhibition.
[d] pLC_{50} is the −log of the molar concentration leading to 50% net cell death.
[e] Refers to the number of cell lines.
[f] MG-MID = mean graph midpoint = arithmetical mean value for all tested cancer cell lines. If the indicated effect was not attainable within the used concentration interval, the highest tested concentration was used for the calculation.

Table 2. Inhibition of in vitro cancer cell lines by compounds **3** and **4**[a]

Cell line	pGI_{50}[b]					
	3a	**3b**	**3c**	**3d**	**4a**	**4b**
Leukemia						
CCRF-CEM	6.54	7.43	7.55	6.61	7.37	6.52
HL-60(TB)	6.71	7.57	7.57	6.79	7.50	6.79
K-562	6.74	7.51	7.46	6.99	7.45	7.43
MOLT-4	6.56	6.84	7.18	6.08	7.41	6.46
RPMI-8226	6.60	7.45	7.62	6.50	nd[c]	6.50
SR	nd	nd	6.85	6.38	nd	5.85
Non-small cell lung cancer						
A549/ATCC	5.44	5.90	6.31	5.47	6.10	5.43
EKVX	4.87	5.58	5.76	5.46	5.95	4.98
HOP-62	5.62	5.72	6.58	5.77	5.45	5.36
HOP-92	nd	nd	>8.00	6.95	7.26	6.79
NCI-H226	5.35	nd	nd	5.49	6.46	4.57
NCI-H23	6.34	6.75	6.76	6.24	7.55	6.13
NCI-H322M	4.95	5.60	5.85	5.59	5.66	5.78
NCI-H460	5.21	5.62	5.84	5.41	5.71	5.24
NCI-H522	6.34	7.26	7.61	5.98	6.76	6.34
Colon cancer						
COLO 205	6.46	6.59	6.89	5.97	6.83	6.44
HCC-2998	nd	6.01	6.72	5.80	6.89	5.81
HCT-116	6.46	6.50	6.90	5.92	6.22	6.39
HCT-15	6.45	7.32	7.57	nd	7.54	6.42
HT29	6.49	6.54	6.68	5.69	5.73	6.09
KM12	5.56	6.20	6.48	5.92	6.05	5.92
SW-620	6.33	7.25	nd	5.84	nd	6.21
CNS Cancer						
SF-268	5.46	6.45	6.72	5.89	6.58	5.50
SF-295	5.20	5.48	5.77	5.76	nd	5.44
SF-539	5.53	6.44	6.63	5.72	6.46	5.44
SNB-19	4.93	5.58	6.21	5.75	5.52	4.94
SNB-75	nd	nd	nd	nd	5.64	nd
U251	5.22	6.29	nd	4.67	6.00	5.28
Melanoma						
MALME-3M	6.34	6.19	6.65	7.28	>8.00	7.48
M14	6.34	6.59	6.74	5.82	7.15	6.22
SK-MEL-2	nd	nd	nd	nd	6.15	nd
SK-MEL-28	6.55	6.88	6.81	5.92	5.61	6.22
UACC-257	nd	nd	nd	nd	6.99	nd
UACC-62	5.61	6.39	6.66	5.62	6.68	5.50
Ovarian cancer						
IGROV1	5.33	6.28	nd	5.82	nd	5.35
OVCAR-3	6.46	6.59	6.91	6.87	nd	6.75
OVCAR-4	5.32	6.60	6.69	5.63	7.94	5.90
OVCAR-5	5.48	5.75	5.92	5.84	6.63	5.45
OVCAR-8	5.28	6.48	nd	5.64	6.05	5.39
SK-OV-3	6.28	7.05	6.81	5.98	6.52	6.19
Renal cancer						
786-0	6.29	6.40	7.16	5.93	6.52	6.34
A498	5.37	nd	nd	5.63	nd	5.26
ACHN	6.16	6.49	7.24	<4.00	7.38	6.12
CAKI-1	6.35	6.53	6.79	6.07	7.76	6.46
RXF 393	6.17	6.87	7.41	6.18	7.55	6.44
SN12C	5.60	6.45	6.76	5.83	6.63	5.61
TK-10	6.27	6.62	6.76	6.47	7.40	6.95
UO-31	5.18	nd	nd	5.43	5.77	5.27
Prostate cancer						
PC-3	6.37	6.76	7.19	5.94	6.71	6.26
DU-145	5.57	6.37	6.71	5.35	nd	5.37
Breast cancer						
MCF7	6.47	6.55	7.00	5.99	6.60	6.43

Table 2 (*continued*)

Cell line	pGI_{50}[b]					
	3a	**3b**	**3c**	**3d**	**4a**	**4b**
NCI/ADR-RES	5.67	6.60	6.66	5.82	7.17	5.69
MDA-MB-231/ATCC	nd	nd	nd	nd	6.85	nd
HS 578T	4.92	6.54	nd	5.50	6.42	5.21
MDA-MB-435	6.54	6.71	6.75	5.97	7.15	6.68
BT-549	5.95	6.34	6.54	5.89	>8.00	5.61
T-47D	5.03	5.22	5.64	5.41	7.27	5.23
MG-MID[d]	5.88	6.48	6.78	5.89	6.71	5.95

[a] Data obtained from the NCI's in vitro disease-oriented human tumor cell screen.
[b] pGI_{50} is the −log of the molar concentration causing 50% growth inhibition of tumor cells.
[c] Not determined.
[d] MG-MID = mean graph midpoint = arithmetical mean value for all tested cancer cell lines. If the indicated effect was not attainable within the used concentration interval, the highest tested concentration was used for the calculation.

It was found that when there is the same group on the arsenic atom, such as **3a** and **4a**–**b**, the substituents on oxygen affect its activity. When the hydroxyl groups are acetylated the pLC_{50} MG-MID value is 4.91 instead of 4.34. But when it is a much bulkier group as in 2-chloro-2-phenylacetyl, the pLC_{50} MG-MID value is 4.36. This is similar to that observed with the unsubstituted compound.

In Table 2 are reported the pGI_{50} values of derivatives **3** and **4**. Most display anticancer activities having GI_{50} values in the low micromolar or sub-micromolar concentration range. It is notable that the pGI_{50} MG-MID values of leukemia sub-panel are always higher than the overall cell line MG-MID values (ΔMG-MID 0.07–1.48), with the exception of **4b** in *SR* cell line (ΔMG-MID − 0.1), which means that arsenic derivatives are effective against the leukemia sub-panel; and the pGI_{50} MG-MID values of CNS cancer sub-panel are always lower than the overall cell line MG-MID values (ΔMG-MID 0 to −1.22), which suggests that arsenic derivatives are less effective against the CNS cancer sub-panel.

In Table 3 are reported the pLC_{50} of **3a**–**3d** and **4a**,**4b**. At LC_{50} level the most interesting compound is **3c** in terms of pLC_{50} (MG-MID = 5.52) followed by **4a**, **3b**, **3d**, **4b**, and **3a** (MG-MID in the range 4.34–4.91). It is noted that **3c** has good anticancer activity in the leukemia, renal and prostate cancer sub-panels. For example, in the leukemia sub-panels, LC_{50} values to *HL-60*(*TB*) and *K*-562 cell lines reached 0.65 and 0.62 μM (in terms of pLC_{50} 6.19 and 6.21). In the renal cancer sub-panel, LC_{50} values to 786–0, *ACHN* cell lines reached 0.48 and 0.43 μM; in the prostate cancer sub-panel, LC_{50} value to *PC-3* cell line is 0.44 μM. Compound **3c** has good selectivity in leukemia (the pLC_{50} of cell lines in leukemia sub-panel is below 4.00 except for *HL-60(TB)* and *K*-562 cell lines).

A comparison of the in vitro activity of the compounds reported herein shows that they have only slightly stronger activity than the glutathione analogue. The latter is currently undergoing Phase II clinical trials.

3. Conclusion

In summary, six *S*-dialkylarsenic compounds have been successfully synthesized in good yield. They were screened for their activity against a panel of about 60 human tumor cell lines. Most of them possess encouraging anticancer activity having GI_{50} values in the low micromolar or sub-micromolar concentration range and most are sensitive to the cell lines in leukemia, renal cancer, and prostate cancer. The di-*n*-propyl arsenic derivative, **3c**, shows the greatest activity in terms of LC_{50} values.

4. Experimental

4.1. General

All melting points were taken on a Buchi-Tottoli capillary apparatus and are uncorrected; ^1H and ^{13}C NMR spectra were measured in $CDCl_3$ solution, unless otherwise specified (TMS as internal reference), at 300 and 75 MHz, using a Varian 300 NMR spectrometer. The high resolution mass spectra (HRMS) measurements were obtained using a Kratos MS80 mass spectrometer. Column chromatography was performed on Merck silica gel 230–400 mesh ASTM. Microanalyses were in agreement with theoretical values (0.4%). Elemental analyses were performed by the Galbraith Laboratories, Knoxville, Tenn.

4.2. General procedure for the synthesis of *S*-(dialkylarsino)-3-mercapto-1,2-propanediol (3a–d)

To a solution of 3-mercapto-1,2-propanediol (2.16 g, 20.0 mmol) in chloroform, dialkyliodoarsine (21.0 mmol) was added at room temperature. After stirring for about 5 min, a solution of Et_2NH (24.0 mmol) in chloroform was added dropwise. The reaction mixture was stirred for 4 h then was filtered. The filtrate was washed with water (except **3a**, because **3a** is soluble in water) and dried over Na_2SO_4 to form the crude product in about 90% yield. The crude product was separated by evaporation under reduced pressure or by silica gel column chromatography (**3a**).

S-(Dimethylarsino)-3-mercapto-1,2-propanediol (**3a**), liquid. ^1H NMR ($CDCl_3$): δ 1.38 (s, 6H, CH_3), 2.57

Table 3. Inhibition of in vitro cancer cell lines by compounds **3** and **4**[a]

Cell line	pLC_{50}[b]					
	3a	**3b**	**3c**	**3d**	**4a**	**4b**
Leukemia						
CCRF-CEM	4.33	nd[c]	nd	5.25	<4.00	4.49
HL-60(TB)	5.23	6.11	6.19	5.27	4.16	5.07
K-562	5.41	5.48	6.21	6.00	nd	5.27
MOLT-4	4.70	<4.00	<4.00	5.00	<4.00	<4.00
RPMI-8226	<4.00	<4.00	nd	nd	nd	<4.00
SR	nd	nd	<4.00	<4.00	nd	<4.00
Non-small cell lung cancer						
A549/ATCC	4.43	5.18	4.85	<4.00	<4.00	<4.00
EKVX	4.07	<4.00	<4.00	<4.00	4.40	<4.00
HOP-62	4.51	4.65	5.61	5.22	4.45	4.39
HOP-92	nd	nd	6.83	5.33	5.33	4.39
NCI-H226	4.35	nd	nd	4.42	5.03	4.17
NCI-H23	4.63	6.21	6.19	5.35	5.58	4.64
NCI-H322M	4.27	4.58	5.28	4.81	4.61	4.49
NCI-H460	4.13	4.51	5.08	4.25	4.34	4.10
NCI-H522	<4.00	5.65	4.91	nd	4.76	<4.00
Colon cancer						
COLO 205	4.34	4.62	nd	5.20	5.02	<4.00
HCC-2998	nd	5.31	6.05	5.27	6.18	5.09
HCT-116	nd	4.04	6.30	5.31	5.36	5.31
HCT-15	<4.00	5.21	5.93	nd	5.54	<4.00
HT29	4.33	4.28	nd	nd	<4.00	<4.00
KM12	4.24	4.71	5.19	5.30	4.72	4.51
SW-620	4.08	5.45	nd	nd	nd	<4.00
CNS cancer						
SF-268	4.23	5.35	5.38	5.20	4.61	4.25
SF-295	4.26	4.38	5.21	4.68	nd	4.36
SF-539	4.29	5.15	5.50	5.12	<4.00	<4.00
SNB-19	4.21	4.34	5.21	nd	4.12	4.07
SNB-75	nd	nd	nd	nd	4.39	nd
U251	<4.00	5.22	nd	<4.00	4.94	<4.00
Melanoma						
MALME-3M	4.64	5.12	5.74	5.56	5.79	5.47
M14	4.40	5.44	5.90	5.26	5.46	4.46
SK-MEL-2	nd	nd	nd	nd	<4.00	nd
SK-MEL-28	5.26	4.41	6.19	nd	4.23	nd
UACC-257	nd	nd	nd	nd	nd	nd
UACC-62	<4.00	<4.00	<4.00	<4.00	nd	<4.00
Ovarian cancer						
IGROV1	<4.00	4.58	nd	nd	nd	<4.00
OVCAR-3	4.45	5.27	nd	5.63	nd	5.49
OVCAR-4	<4.00	<4.00	<4.00	<4.00	5.60	<4.00
OVCAR-5	4.47	5.23	5.30	5.28	5.60	4.43
OVCAR-8	4.18	nd	nd	<4.00	4.23	<4.00
SK-OV-3	<4.00	<4.00	nd	<4.00	4.42	<4.00
Renal cancer						
786-0	5.18	5.28	6.32	5.31	5.42	4.60
A498	4.12	nd	nd	5.03	nd	4.24
ACHN	<4.00	5.44	6.37	<4.00	5.98	4.41
CAKI-1	4.46	5.42	6.06	5.34	5.96	4.52
RXF 393	4.39	5.50	6.28	5.34	5.49	4.44
SN12C	4.09	nd	6.25	nd	5.46	4.17
TK-10	4.55	5.45	6.20	5.41	5.63	5.57
UO-31	<4.00	<4.00	<4.00	<4.00	<4.00	<4.00
Prostate cancer						
PC-3	4.41	5.44	6.36	5.25	5.01	4.32
DU-145	4.37	5.35	6.09	4.24	nd	4.23
Breast cancer						
MCF7	4.27	5.45	nd	5.27	5.35	4.17

Table 3 (*continued*)

Cell line	pLC_{50}[b]					
	3a	**3b**	**3c**	**3d**	**4a**	**4b**
NCI/ADR-RES	4.45	5.57	5.79	5.11	5.43	4.49
MDA-MB-231/ATCC	nd	nd	nd	nd	5.58	nd
HS 578T	<4.00	<4.00	nd	<4.00	4.13	<4.00
MDA-MB-435	4.30	5.20	6.03	5.32	5.52	4.54
BT-549	4.43	5.13	nd	5.22	5.33	4.19
T-47D	4.13	4.35	5.15	<4.00	nd	4.22
MG-MID[d]	4.34	4.91	5.52	4.85	4.91	4.36

[a] Data obtained from the NCI's in vitro disease-oriented human tumor cell screen.
[b] pLC_{50} is the −log of the molar concentration leading to 50% net cell death.
[c] Not determined.
[d] MG-MID = mean graph midpoint = arithmetical mean value for all tested cancer cell lines. If the indicated effect was not attainable within the used concentration interval, the highest tested concentration was used for the calculation.

(s, 2H, OH), 2.73 (dd, J = 7.5, 13.8 Hz, C*H*H), 2.80 (dd, J = 7.5, 13.8 Hz, CH*H*). 3.58 (dd, J = 6.7, 12.5 Hz, 1H, CH), 3.73-3.81 (m, 2H, CH_2). ^{13}C NMR ($CDCl_3$): δ 14.02, 14.44, 35.21, 65.09, 72.12. MS (EI): 219 (M+Li), 185, 183, 153, 102. Anal. Calcd. for $C_5H_{13}AsO_2S$: C, 28.31; H, 6.18; As, 35.32; S, 15.12. Found: C, 28.66; H, 6.23; As, 34.98; S, 15.03.

S-(Diethylarsino)-3-mercapto-1,2-propanediol (**3b**), liquid. ^1H NMR ($CDCl_3$): δ 1.22 (t, J = 7.5 Hz, 6H, CH_3), 1.67–1.75 (dt, J = 2.4, 7.5 Hz, 4H, CH_2), 2.09–2.14 (m, 2 H, OH), 2.69–2.84 (2dd, J = 6.6, 19.8 Hz, 2H, CH_2), 3.55–3.66 (m, 1H, CH), 3.67–3.73 (m, 2H, CH_2). ^{13}C NMR ($CDCl_3$): δ 10.40, 21.40, 21.45, 35.57, 65.32, 73.99. MS (EI): 247 (M+Li), 247, 179. Anal. Calcd. for $C_7H_{17}AsO_2S$: C, 35.00; H, 7.13; As, 31.19; S, 13.35. Found: C, 35.42; H, 7.22; As, 31.11; S, 13.27.

S-(Di-*n*-propylarsino)-3-mercapto-1,2-propanediol (**3c**), liquid. ^1H NMR ($CDCl_3$): δ 1.01 (m, 6H, CH_3), 1.56–1.71 (m, 6H, CH_2), 1.78–1.85 (m, 2H, CH_2), 2.52 (s, 2H, OH), 2.76-2.79 (m, 2H, CH_2), 3.57 (dd, J = 6.9, 12.3 Hz, 1H, CH), 3.74–3.79 (m, 2H, CH_2). ^{13}C NMR ($CDCl_3$): δ 16.20, 19.76, 31.59, 31.64, 35.63, 65.11, 72.08. MS (EI): 269 (M+1), 179. Anal. Calcd. for $C_9H_{21}AsO_2S$: C, 40.30; H, 7.89; As, 27.93; S, 11.95. Found: C, 40.51; H, 7.79; As, 28.21; S, 11.86.

S-(Diisopropylarsino)-3-mercapto-1,2-propanediol (**3d**), liquid. ^1H NMR (d_6-acetone): δ 1.18 (dd, J = 0.75, 7.8 Hz, 6H, CH_3), 1.26 (dd, J = 0.75, 7.8 Hz, 6H, CH_3), 1.97–2.09 (m, 2H, CH), 2.64–2.83 (2dd, J = 6.0, 15.6 Hz, 2H), 2.85–3.04 (m, 1H, CH), 3.51–3.58 (m, 2H), 3.62–3.72 (m, 2H). ^{13}C NMR (d_6-acetone): δ 20.04, 20.27, 27.44, 36.20, 65.33, 74.00. MS (EI): 275 (M+Li), 221, 195. Anal. Calcd. for $C_9H_{21}AsO_2S$: C, 40.30; H, 7.89; As, 27.93; S, 11.95. (Note, this compound is not very stable, and decomposes slowly at room temperature.)

4.3. The synthesis of *S*-(dimethylarsino)-3-mercapto-1,2-propyl diacetate (4a)

To a solution of **3a** (2.12 g, 10.0 mmol) and pyridine (excess) in dry chloroform was added Ac_2O (2.45 g, 24.0 mmol). The mixture was stirred for 10 h at room temperature. Then it was evaporated to remove the solvent. The mixture was purified by flash column chromatography or evaporation to get product **4a** (2.42 g, 82% yield). Liquid. ^1H NMR ($CDCl_3$): δ 1.36 (d, J = 2.4 Hz, 6H, $AsCH_3$), 2.08 (s, 3H, $COCH_3$), 2.09 (s, 3H, $COCH_3$), 2.88 (dd, J = 3.6, 6.0 Hz, 2H, CH_2), 4.20 (dd, J = 6.0, 12.0 Hz, 1H, C*H*H), 4.35 (dd, J = 3.6, 12.0 Hz, 1H, CH*H*), 5.08–5.15 (2dd, J = 3.6, 6.0 Hz, 1 H, CH). ^{13}C NMR ($CDCl_3$): δ 14.55, 14.60, 21.02, 21.30, 32.04, 63.73, 72.35, 170.43, 170.86. MS (EI): 167, 153. Anal. Calcd. for $C_9H_{17}AsO_4S$: C, 36.49; H, 5.78; As, 25.29; S, 10.83. Found: C, 36.78; H, 5.86; As, 24.93; S, 10.57.

4.4. The synthesis of *S*-(dimethylarsino)-3-mercapto-1,2-propyl di-2-chloro- 2-phenylacetate (4b)

To a solution of **3a** (2.12 g, 10.0 mmol) and pyridine (excess) in dry chloroform was added 2-chloro-2-phenylacetate chloride (4.54 g, 24.0 mmol). The mixture was stirred for another 10 h at room temperature. Then it was evaporated to remove solvent. The mixture was purified by flash column chromatography to yield product **4b** (4.18 g, 81% yield). Low melting point solid. ^1H NMR ($CDCl_3$): δ 1.26 (d, J = 3.9 Hz, 3H, CH_3), 1.32 (d, J = 3.9 Hz, 3H, CH_3), 2.17 (s, 1H), 2.66 (d, J = 6.9 Hz, 1H), 2.81 (d, J = 6.9 Hz, 1H), 4.21–4.51 (m, 2H, CH_2), 5.07–5.33 (m, 2H), 7.34–7.74 (m, 10H, Ph-H). ^{13}C NMR ($CDCl_3$): δ 14.28, 14.30, 14.34, 30.95, 31.10, 58.69, 58.86, 58.93, 64.53, 64.56, 64.62, 64.66, 73.92, 73.97, 127.89, 127.93, 127.97, 128.00, 128.85, 128.90, 128.93, 129.37, 129.42, 135.36, 167.48, 167.58, 167.72, 167.87. MS (EI): 465, 401, 373, 327, 295, 267. Anal. Calcd. for $C_{21}H_{23}AsCl_2O_4S$: C, 48.76; H, 4.48; As, 14.48; S, 6.20; Cl, 13.71. Found: C, 48.89; H, 4.53; As, 14.25; S, 6.11; Cl, 13.84.

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