A report of the activities

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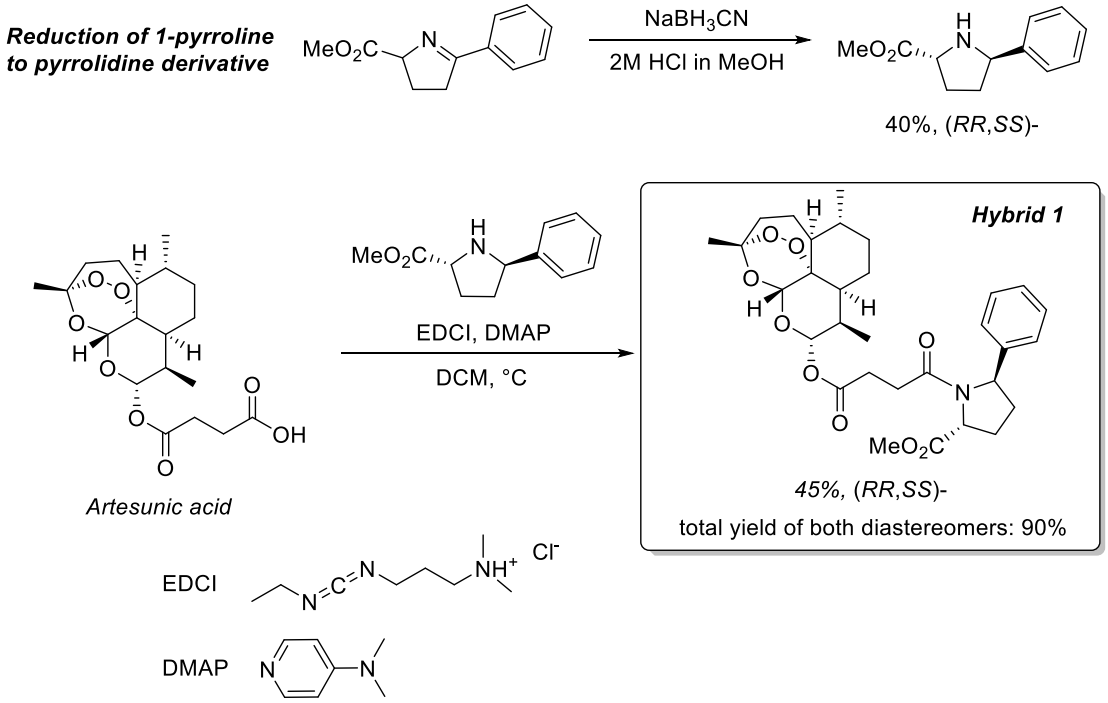
Funding decision on Proposal: F-2021b-24_r

Title: Synthesis and biological activity of novel 1-pyrrolines and their artemisinin hybrids

Principle Investigator: Prof. Dr. Svetlana Tsogoeva

Head of the Partner Group in Russia: Dr. Nikolai Rostovskii

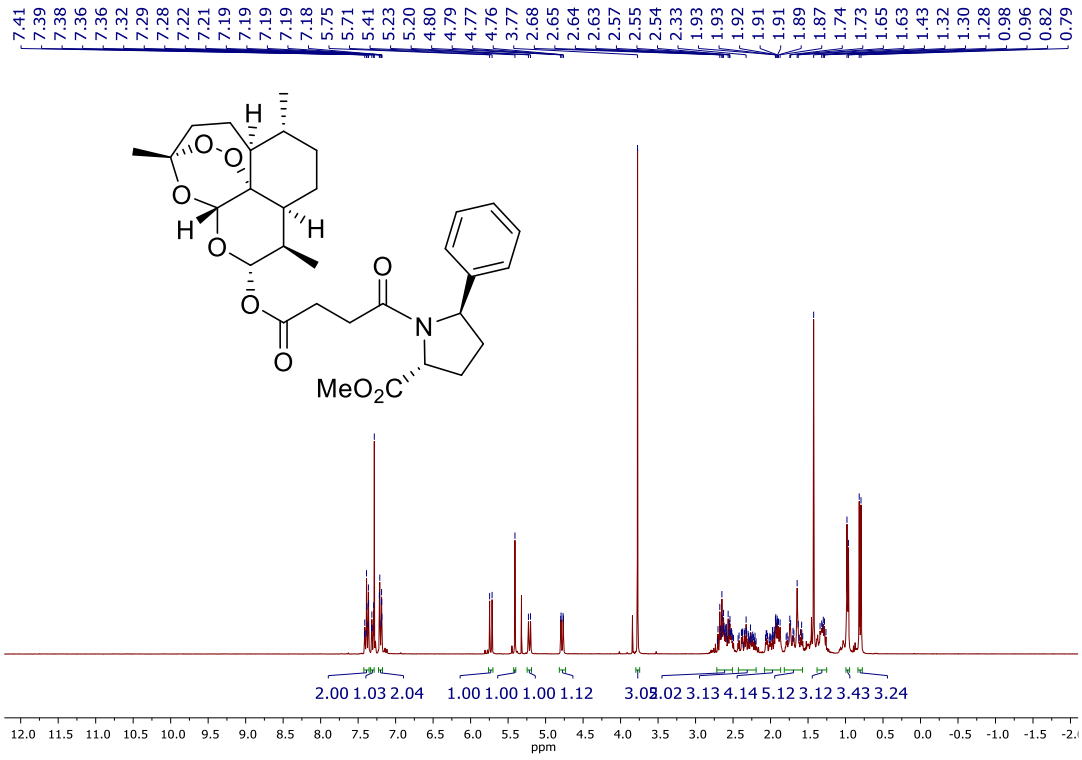
Part I. Hybrids synthesis

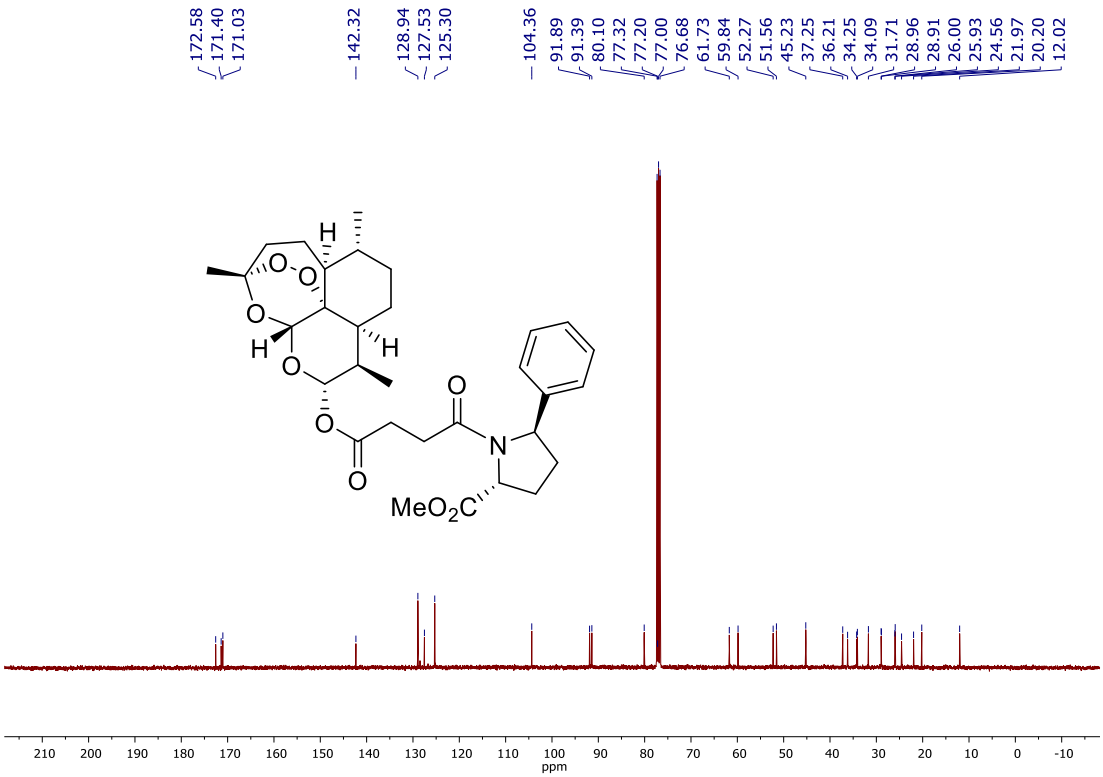


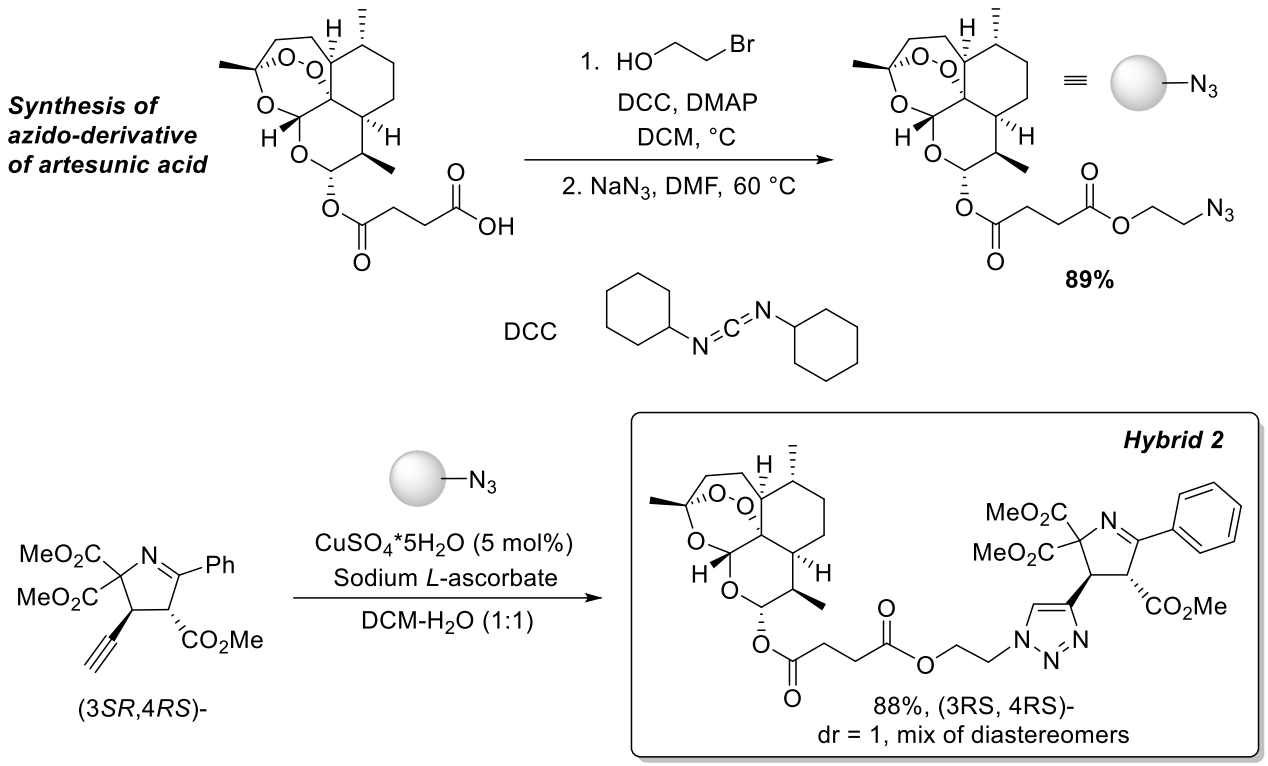
Starting pyrrolidine derivative was synthesized according to literature procedure (*Org. Biomol. Chem.*, **2012**, *10*, 7863-7868).

Hybrid 1 (45%, methyl (2*R*,5*R*)-1-(4-oxo-4-(((3*R*,5*aS*,6*R*,8*aS*,9*R*,10*S*,12*R*,12*aR*)-3,6,9-trimethyldecahydro-12*H*-3,12-epoxy[1,2]dioxepino[4,3-*i*]isochromen-10-yl)oxy)butanoyl)-5-phenylpyrrolidine-2-carboxylate) was synthesized according to procedure (*Angew. Chem*. **2019**, *58* (37), 13066–13079) as a separated diastereomer. White solid. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.42 – 7.36 (m, 2H), 7.32 – 7.28 (m, 1H), 7.22 – 7.19 (m, 2H), 5.73 (d, *J* = 9.8 Hz, 1H), 5.41 (s, 1H), 5.22 (d, *J* = 8.2 Hz, 1H), 4.78 (dd, *J*

= 9.3, 1.2 Hz, 1H), 3.77 (s, 3H), 2.76 – 2.49 (m, 5H), 2.43 – 2.17 (m, 3H), 2.07 – 1.87 (m, 4H), 1.82 – 1.57 (m, 5H), 1.43 (s, 3H), 1.38 – 1.25 (m, 3H), 0.97 (d, *J* = 5.8 Hz, 3H), 0.81 (d, *J* = 7.1 Hz, 3H). $^{13}C\{^{1}H\}$ NMR (101 MHz, Chloroform-*d*) δ 172.6, 171.4, 171.0, 142.3, 129.0, 127.5, 125.3, 104.4, 91.9, 91.4, 80.1, 61.7, 59.8, 52.3, 51.6, 45.2, 37.3, 36.2, 34.3, 34.1, 31.7, 29.0, 28.9, 26.0, 25.9, 24.6, 22.0, 20.2, 12.0. HRMS (APPI): calcd for $C_{31}H_{41}NNaO_9^+$, $[M+Na]^+$: 594.2674; found: 594.2687.



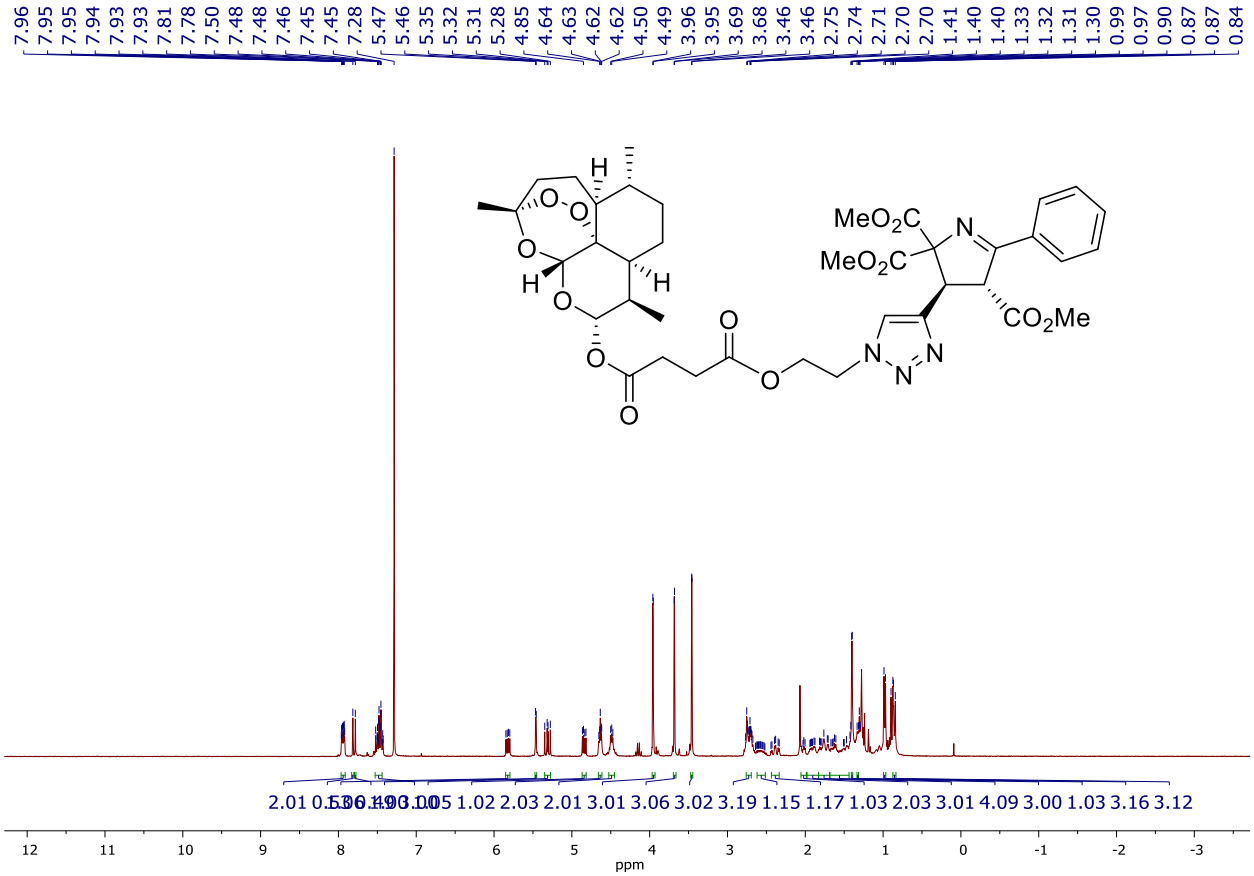


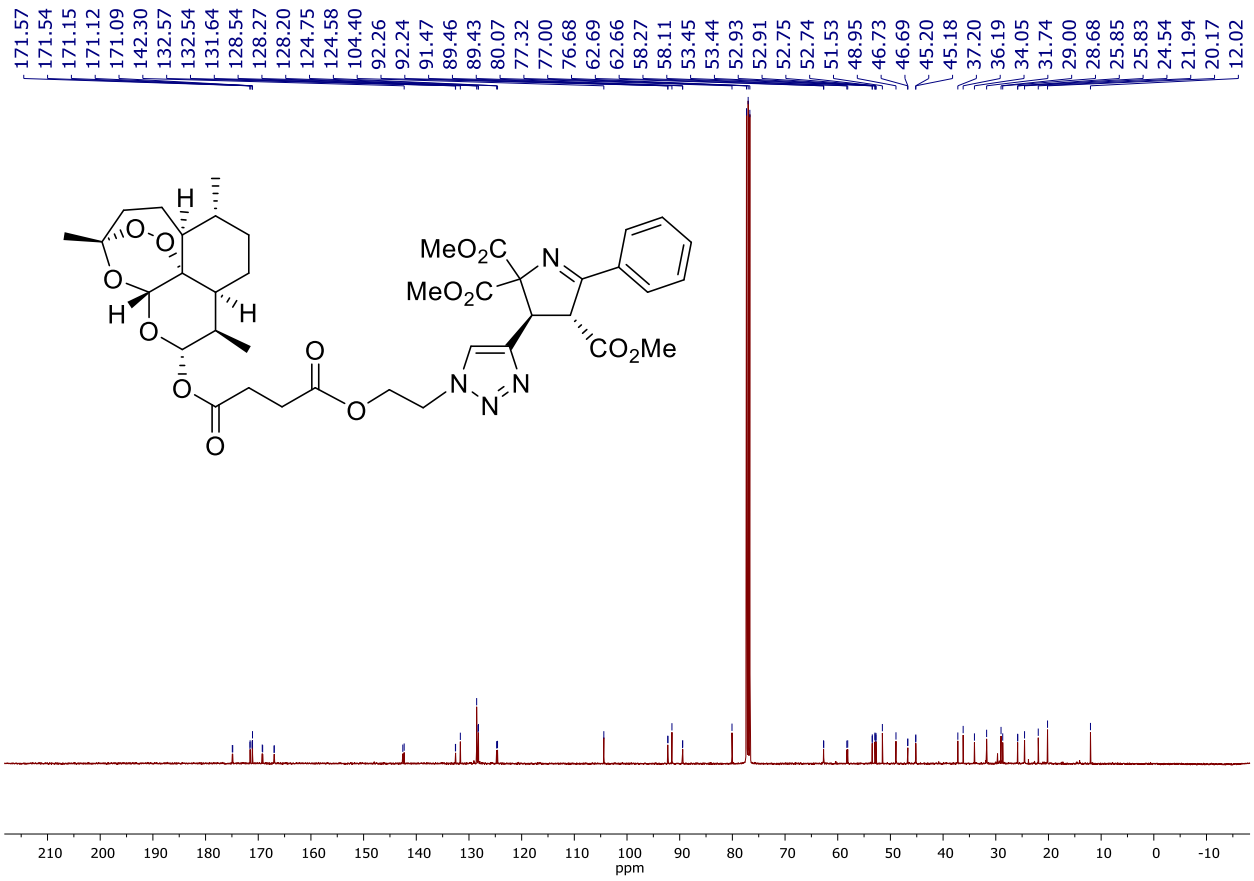


Azido-derivative of the artesunic acid was synthesized according to literature procedure (*Angew. Chem*. **2019**, *58* (37), 13066–13079).

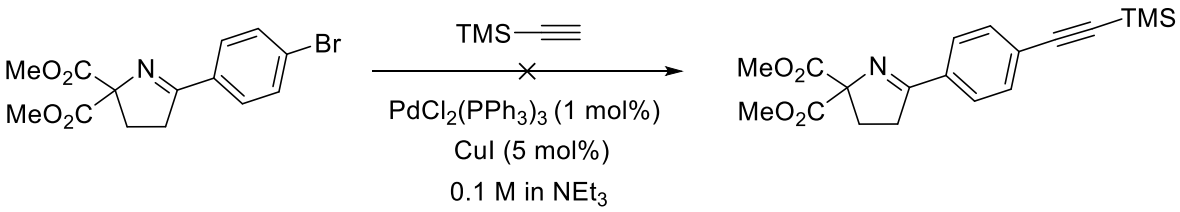
Hybrid 2 (88%, trimethyl (3*R*,4*R*)-3-(1-(2-((4-oxo-4-(((3*R*,5*aS*,6*R*,8*aS*,9*R*,10*S*,12*R*,12*aR*)-3,6,9-trimethyldecahydro-12*H*-3,12-epoxy[1,2]dioxepino[4,3-*i*]isochromen-10-yl)oxy)butanoyl)oxy)ethyl)-1*H*-1,2,3-triazol-4-yl)-5-phenyl-3,4-dihydro-2*H*-pyrrole-2,2,4-tricarboxylate) was synthesized according to procedure (*Angew. Chem*. **2019**, *58* (37), 13066–13079) as a mixture of diastereomers in 1:1 ratio. White solid. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.96 – 7.92 (m, *4*H), 7.81 (s, 1H), 7.78 (s, 1H), 7.52 – 7.42 (m, 6H), 5.85 – 5.80 (m, *2*H), 5.47 (s, 1H), 5.46 (s, 1H), 5.35 – 2.28 (m, 2H), 4.86 – 4.82 (m, 2H), 4.65 – 4.62 (m, 4H), 4.50 – 4.47 (m, 4H), 3.96 (s, 3H), 3.95 (s, 3H), 3.69 (s, 3H), 3.68 (s, 3H), 3.46 (m, 6H), 2.77 – 2.69 (m, 6H), 2.58 (ddt, *J* = 17.2, 10.0, 3.8 Hz, 2H), 2.39 (td, *J* = 13.8, 3.9 Hz, 2H), 2.03 – 2.00 (m, 2H), 1.94 – 1.88 (m, 4H), 1.82 – 1.69 (m, 6H), 1.68 – 1.43 (m, 8H), 1.41 – 1.39 (m, 6H), 1.34 – 1.31 (m, 2H), 0.99 – 0.97 (m, 6H), 0.90 – 0.84 (m, 6H). ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 174.9, 174.8, 171.8, 171.5, 171.2, 171.12, 171.09, 169.24, 169.16, 166.99, 166.97, 142.6, 142.30, 132.6, 132.5, 131.6, 128.5, 128.3, 128.2, 124.8, 124.6, 104.4, 92.3, 92.2, 91.5, 89.5, 89.4, 80.1, 62.69, 62.66, 58.3, 58.1, 53.5, 53.4, 52.93, 52.91, 52.8, 52.7, 51.5,

49.0, 46.73, 46.69, 45.20, 45.18, 37.2, 36.2, 34.1, 31.7, 29.0, 28.7, 25.9, 25.8 24.5, 21.9, 20.2, 12.0. HRMS (APPI): calcd for $C_{39}H_{48}KN_4O_{14}^+$, $[M+K]^+$: 835.2799; found: 835.2810.



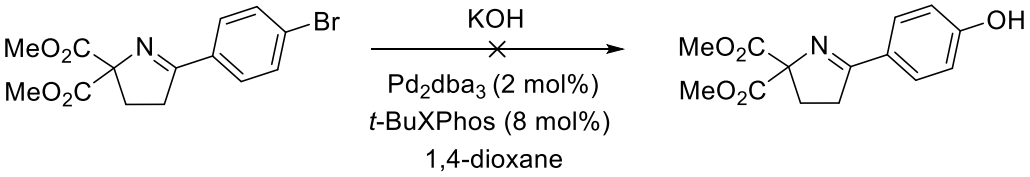


Attempts to synthesis 1-pyrroline with another location of triple bond:

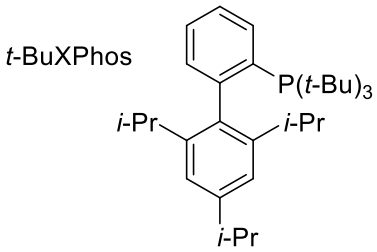


1. Shlenk flask, screwed vial - no reaction
2. 0.1 M THF solution in place of NEt_3 as a solvent - no reaction

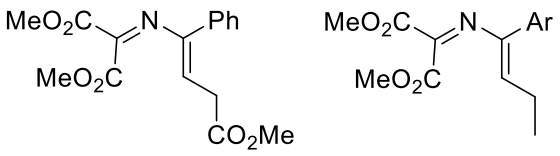
Attempt to introduce hydroxy-group instead of bromine atom:



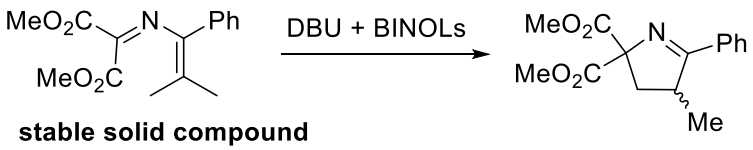
Shlenk flask, freeze-pump-thaw operation - no reaction



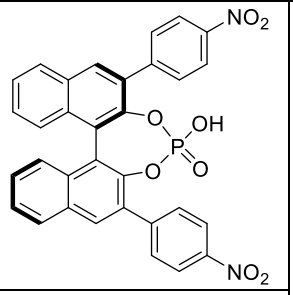
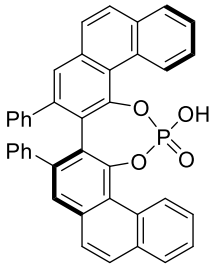
Part II. Enantioselective study of cyclization of 2-azabuta-1,3-dienes to 1-pyrrolines



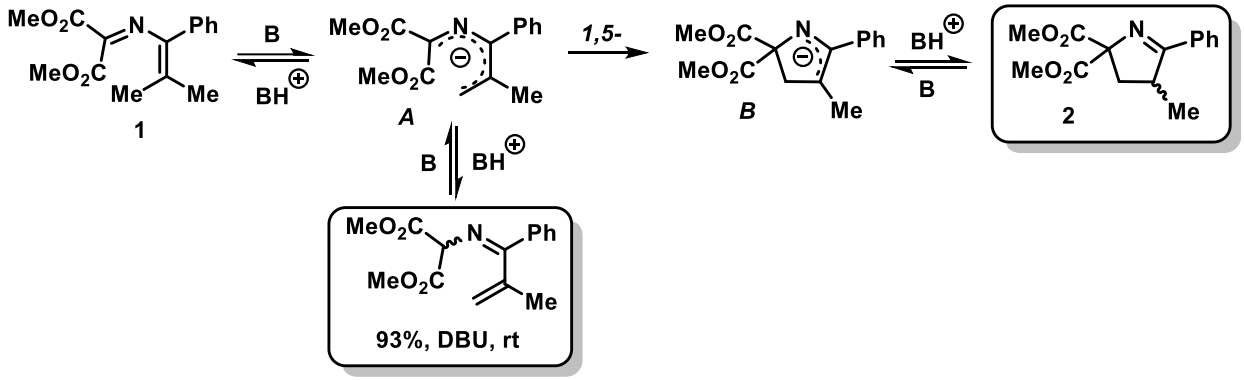
These azabutadienes were synthesized, but were not tested in enantioselective reactions because of lack of internship time



stable solid compound

	BINOL-phosphate	Conditions	Reagents	ee	Reaction time
1		DCE, 100 °C	1:1 DBU+BINOL (1 eq. DBU)	1%	1 h (without BINOLs – 10 min)
2					
3	none		Quinine (1. eq.)		20 h

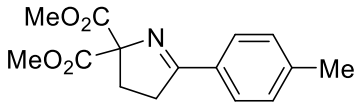
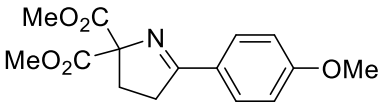
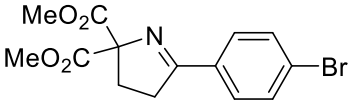
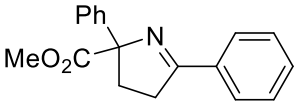
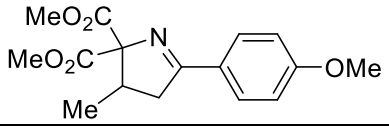
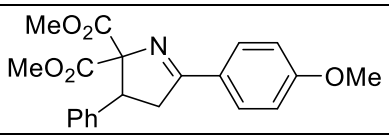
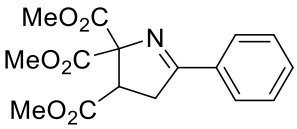
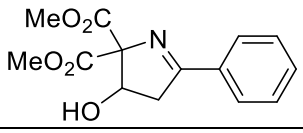
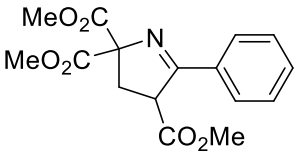
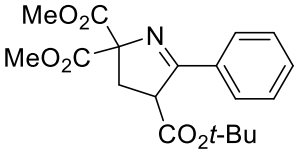
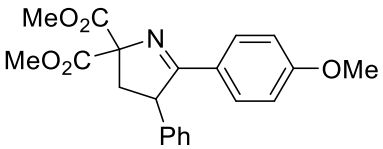
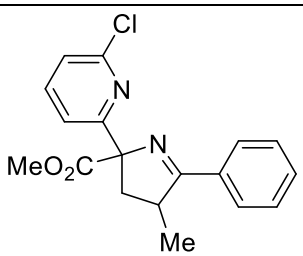
Proposed reaction mechanism

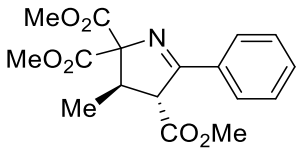
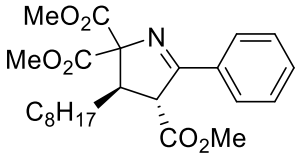
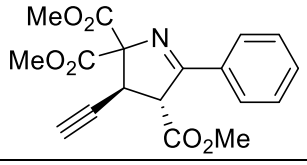
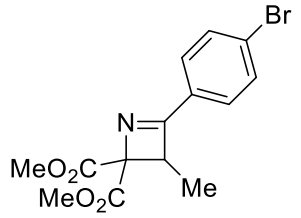
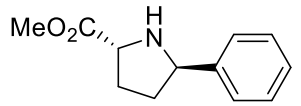
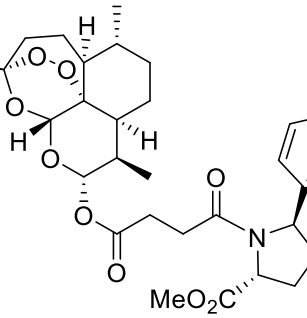
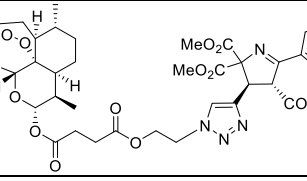


Part III. Biological activity study of 1-pyrrolines and their derivatives.

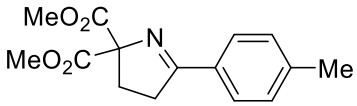
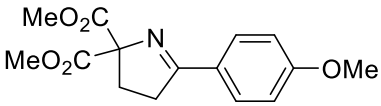
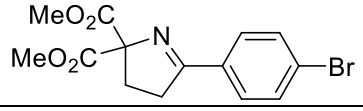
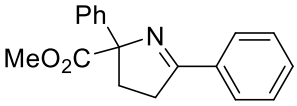
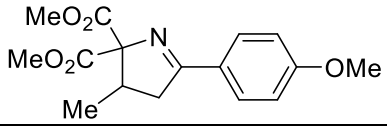
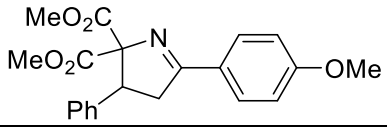
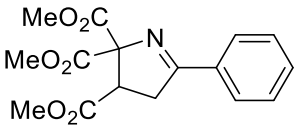
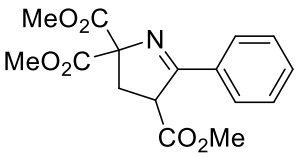
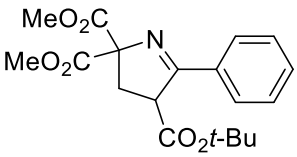
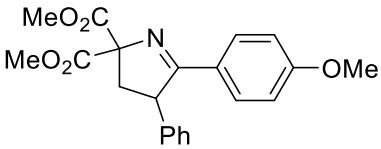
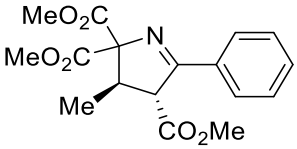
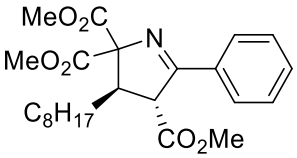
Two sets of samples for antimalarial and anticancer study were sent to collaborators of Prof. Dr. Svetlana Tsogoeva. The lists of compounds and the purity data for them are below. The results are waited for.

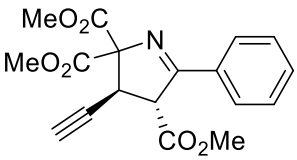
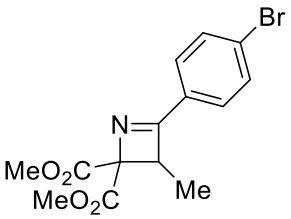
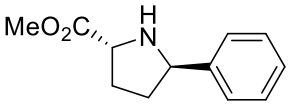
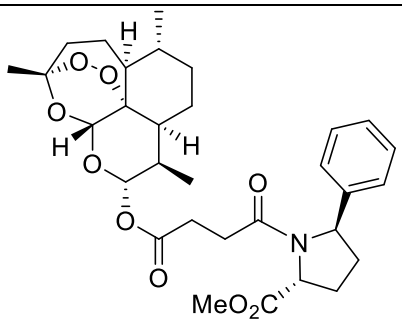
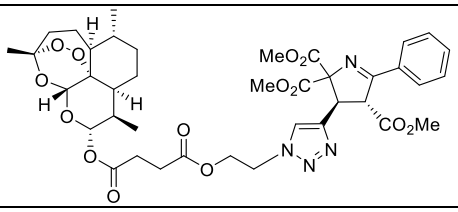
SET 1

N	Structure	Formula	HRMS			EA	
			Calcd/found for	Calcd	Found	Calcd (C/H/N in %)	Found (C/H/N in %)
1		$C_{15}H_{17}NO_4$	$[M+H]^+$	276.1230	276.1235	65.44/ 6.22/ 5.09	65.35/ 6.39/ 4.84
2		$C_{15}H_{17}NO_5$	$[M+H]^+$	292.1180	292.1185	61.85/ 5.88/ 4.81	61.62/ 6.06/ 4.58
3		$C_{14}H_{14}BrNO_4$	$[M+H]^+$	340.0179	340.0180	49.43/ 4.15/ 4.12	49.30/ 4.20/ 4.23
4		$C_{18}H_{17}NO_2$	$[M+H]^+$	280.1332	280.1336	77.40/6.13/ 5.01	76.77/ 6.34/ 4.82
5		$C_{16}H_{19}NO_5$	$[M+H]^+$	306.1336	306.1339	62.94/ 6.27/ 4.59	62.10/ 6.10/ 4.40
6		$C_{21}H_{21}NO_5$	$[M+H]^+$	368.1493	368.1493	68.65/ 5.76/ 3.81	68.35/ 6.05/ 3.66
7		$C_{16}H_{17}NO_6$	$[M+H]^+$	320.1129	320.1132	60.18/ 5.37/ 4.39	59.98/ 5.45/ 4.22
8		$C_{14}H_{15}NO_5$	$[M+H]^+$	278.1023	278.1025	60.64/ 5.45/ 5.05	59.51/ 5.31/ 4.84
9		$C_{16}H_{17}NO_6$	$[M+H]^+$	320.1129	320.1131	60.18/ 5.37/ 4.39	58.70/ 5.50/ 4.28
10		$C_{19}H_{23}NO_6$	$[M+H]^+$	362.1598	362.1599	63.15/ 6.42/ 3.88	62.03/ 6.58/ 3.72
11		$C_{21}H_{21}NO_5$	$[M+H]^+$	368.1493	368.1493	68.65/ 5.76/ 3.81	67.61/ 5.97/ 3.70
12		$C_{18}H_{17}ClN_2O_2$	$[M+H]^+$	329.1051	329.1062	65.75/ 5.21/ 8.52	64.88/ 5.15/ 8.41

13		$C_{17}H_{19}NO_6$	$[M+H]^+$	334.1285	334.1287	61.25/ 5.75/ 4.20	60.09/ 6.01/ 4.03
14		$C_{24}H_{33}NO_6$	$[M+H]^+$	432.2381	432.2382	66.80/ 7.71/ 3.25	63.90/ 7.36/ 3.37
15		$C_{18}H_{17}NO_6$	$[M+H]^+$	344.1129	344.1131	62.97/ 4.99/ 4.08	62.78/ 4.81/ 3.92
16		$C_{14}H_{14}BrNO_4$	$[M+H]^+$	340.0179	340.0184	49.43/ 4.15/ 4.12	49.26/ 3.98/ 3.99
17		$C_{12}H_{15}NO_2$	Previously known compound			70.22/ 7.37/ 6.82	70.01/ 7.21/ 6.59
18		$C_{31}H_{41}NO_9$	$[M+Na]^+$	594.2674	594.2687	65.13/ 7.23/ 2.45	64.91/ 7.02/ 2.34
19		$C_{39}H_{48}N_4O_{14}$	$[M+K]^+$	835.2799	835.2810	58.79/ 6.07/ 7.03	58.65/ 5.91/ 6.80

SET 2

N	Structure	Formula	HRMS			EA	
			Calcd/found for	Calcd	Found	Calcd (C/H/N in %)	Found (C/H/N in %)
1		$C_{15}H_{17}NO_4$	$[M+H]^+$	276.1230	276.1235	65.44/ 6.22/ 5.09	65.35/ 6.39/ 4.84
2		$C_{15}H_{17}NO_5$	$[M+H]^+$	292.1180	292.1185	61.85/ 5.88/ 4.81	61.62/ 6.06/ 4.58
3		$C_{14}H_{14}BrNO_4$	$[M+H]^+$	340.0179	340.0180	49.43/ 4.15/ 4.12	49.30/ 4.20/ 4.23
4		$C_{18}H_{17}NO_2$	$[M+H]^+$	280.1332	280.1336	77.40/6.13/ 5.01	76.77/ 6.34/ 4.82
5		$C_{16}H_{19}NO_5$	$[M+H]^+$	306.1336	306.1339	62.94/ 6.27/ 4.59	62.10/ 6.10/ 4.40
6		$C_{21}H_{21}NO_5$	$[M+H]^+$	368.1493	368.1493	68.65/ 5.76/ 3.81	68.35/ 6.05/ 3.66
7		$C_{16}H_{17}NO_6$	$[M+H]^+$	320.1129	320.1132	60.18/ 5.37/ 4.39	59.98/ 5.45/ 4.22
8		$C_{16}H_{17}NO_6$	$[M+H]^+$	320.1129	320.1131	60.18/ 5.37/ 4.39	58.70/ 5.50/ 4.28
9		$C_{19}H_{23}NO_6$	$[M+H]^+$	362.1598	362.1599	63.15/ 6.42/ 3.88	62.03/ 6.58/ 3.72
10		$C_{21}H_{21}NO_5$	$[M+H]^+$	368.1493	368.1493	68.65/ 5.76/ 3.81	67.61/ 5.97/ 3.70
11		$C_{17}H_{19}NO_6$	$[M+H]^+$	334.1285	334.1287	61.25/ 5.75/ 4.20	60.09/ 6.01/ 4.03
12		$C_{24}H_{33}NO_6$	$[M+H]^+$	432.2381	432.2382	66.80/ 7.71/ 3.25	63.90/ 7.36/ 3.37

13		$C_{18}H_{17}NO_6$	$[M+H]^+$	344.1129	344.1131	62.97/ 4.99/ 4.08	62.78/ 4.81/ 3.92
14		$C_{14}H_{14}BrNO_4$	$[M+H]^+$	340.0179	340.0184	49.43/ 4.15/ 4.12	49.26/ 3.98/ 3.99
15		$C_{12}H_{15}NO_2$	Previously known compound			70.22/ 7.37/ 6.82	70.01/ 7.21/ 6.59
16		$C_{31}H_{41}NO_9$	$[M+Na]^+$	594.2674	594.2687	65.13/ 7.23/ 2.45	64.91/ 7.02/ 2.34
17		$C_{39}H_{48}N_4O_{14}$	$[M+K]^+$	835.2799	835.2810	58.79/ 6.07/ 7.03	58.65/ 5.91/ 6.80