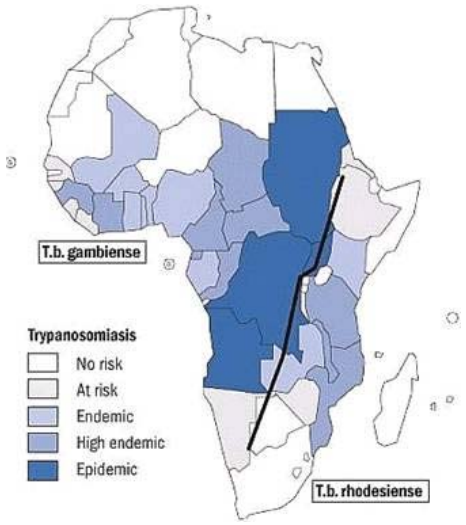
Generation of Anti-trypanosomal Agents Through Concise synthesis and Structural Diversification of Sesquiterpene Analogues

Journal of the American Chemical Society, Article *ASAP*

H. Oguri, T. Hiruma, Y. Yamagishi, H. Oikawa, A. Ishiyama, K. Otoguro, H. Yamada, S. Omura

Human African Trypanosomiasis (HAT)

- Sleeping sickness is transmitted by Tsetse flies that live in 36 sub-Saharan Africa countries



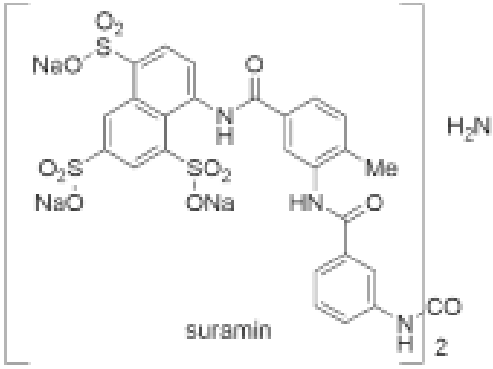
The estimated number of actual cases is currently 30000 (10000 reported)

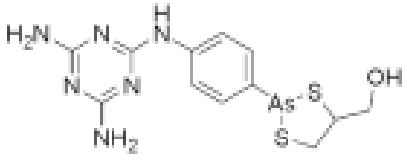
- Infection and Symptoms :

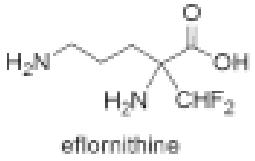
First stage : Parasites multiply in subcutaneaous tissues, blood and lymph causing fever, headhache , joint pains and itching

Second stage : Parasites cross the blood-brain barrier to infect the central nervous system. Changes of behaviour, confusion, poor coordination, disturbance in the sleeping cycle.

Four drugs approved for the treatment of HAT

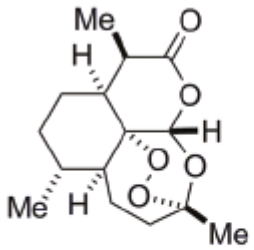






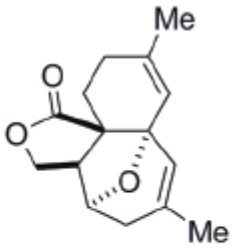
⇨ Difficult to apply, undesirable side-effects, resistance to drugs has been observed

Some interesting Ca2+-ATPases inhibitors that exhibit anti-trypanosomal activities



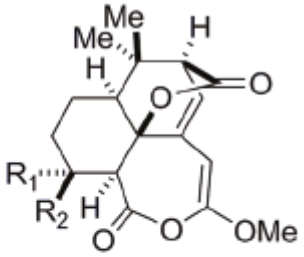
artemisinin (**1**)

5.8 μg/mL



anthecularin (**2**)

10.1 μg/mL

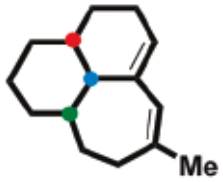


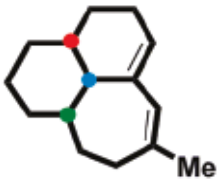
transtaganolide C (**3**)
R_1 = vinyl, R_2 = Me
transtaganolide D (**4**)
R_1 = Me, R_2 = vinyl

Not reported

Structural similarities :
- Tricycles scaffold
- Diene motif
- Methyl substituents on the 7-membered ring

Design of a model



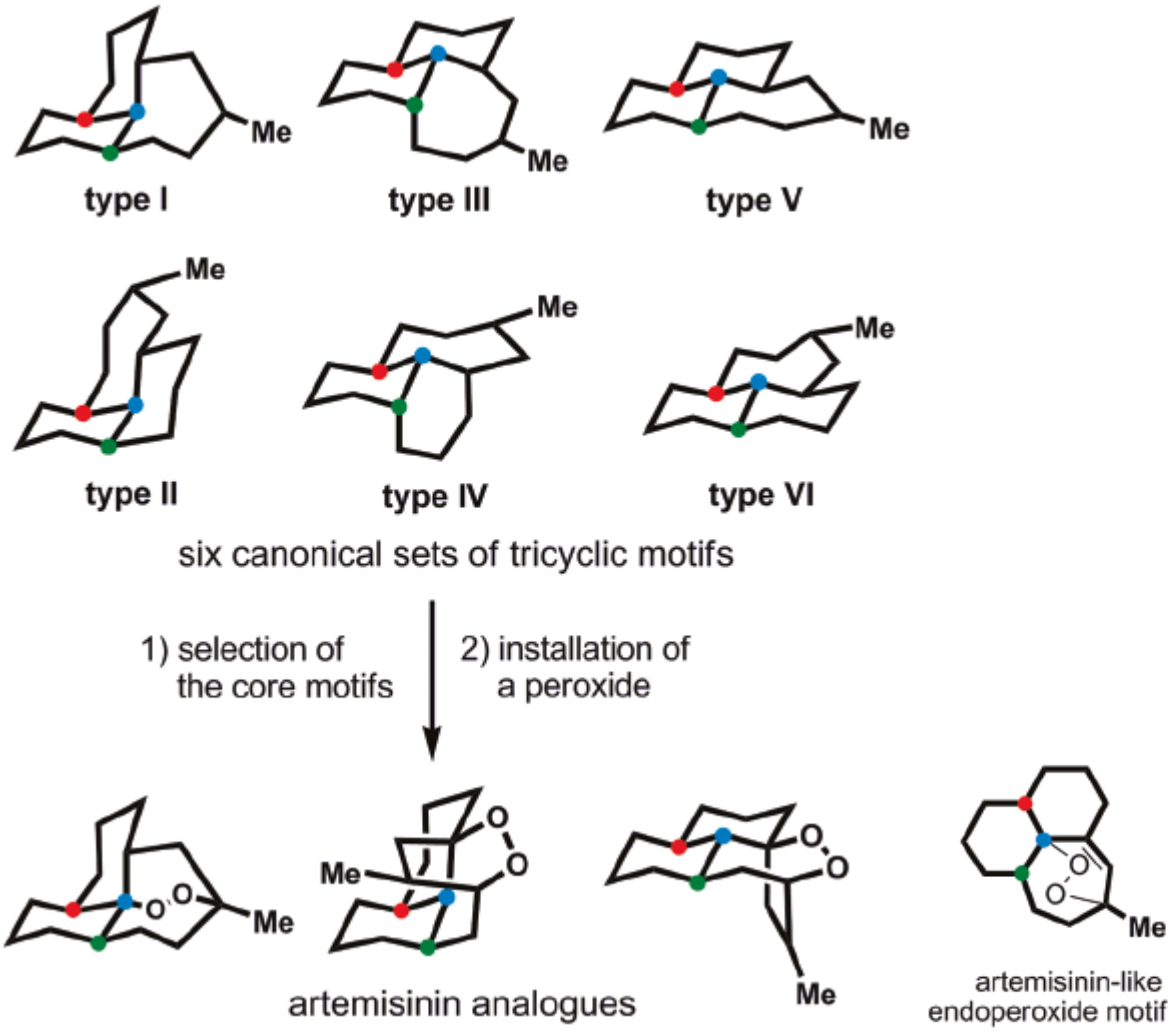


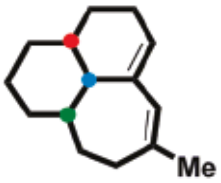
Design of structural motifs

2 factors that regulate molecular architecture :

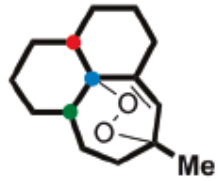
- 3 variations for the 3 consecutives sp3 ring junction :cis-cis, trans-cis and trans-trans

- 2 arrays of the 7-membered ring against the ring junction

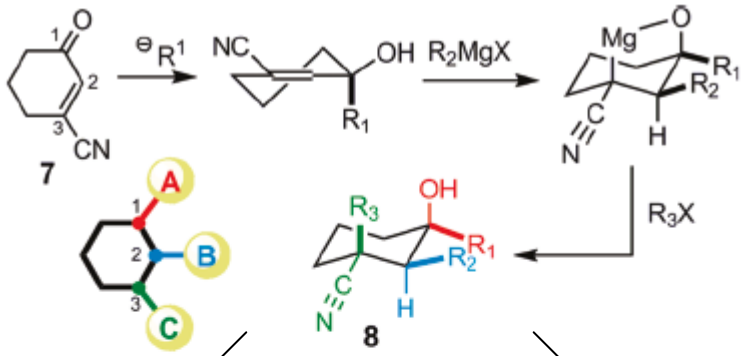


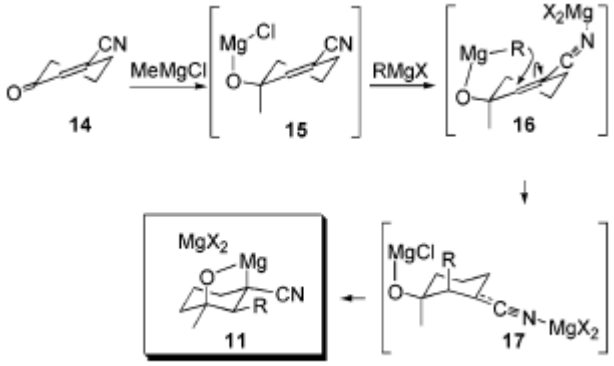


Design of a synthetic process

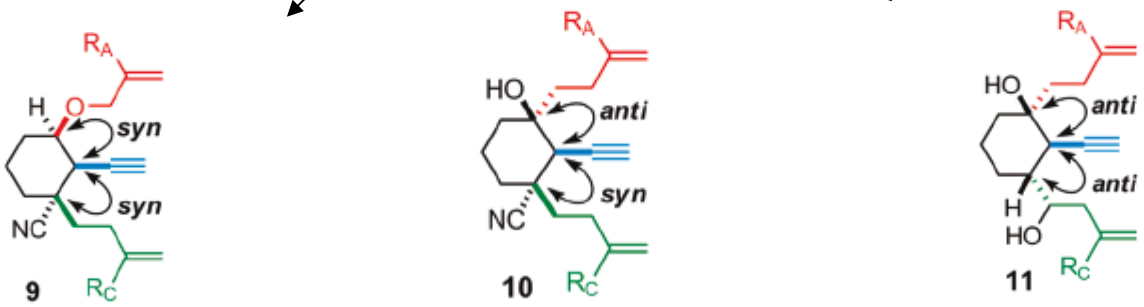


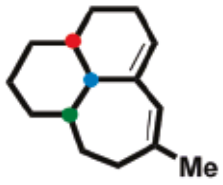
artemisinin-like
endoperoxide motif



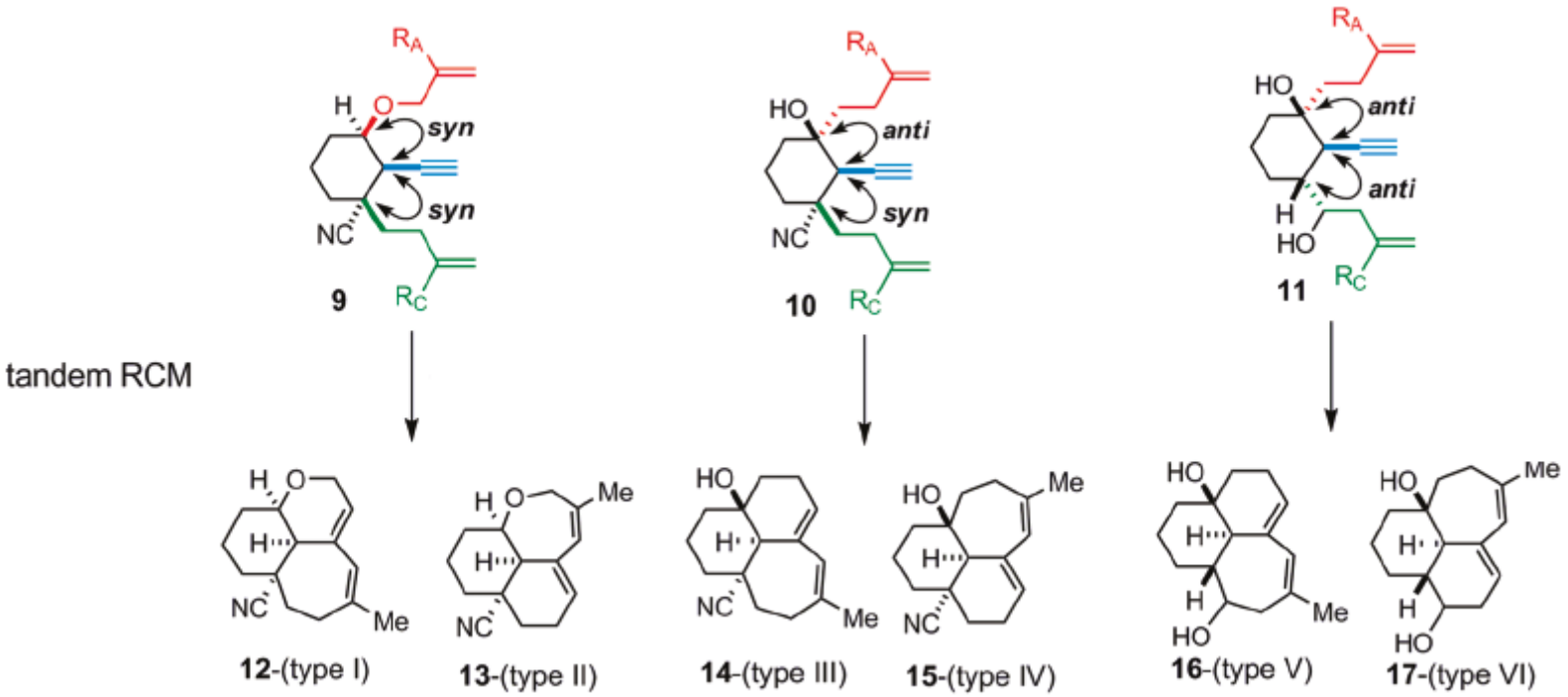


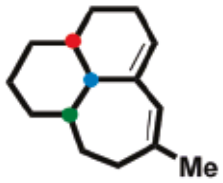
J. Org. Chem. **2006**, *71*, 1430−1435



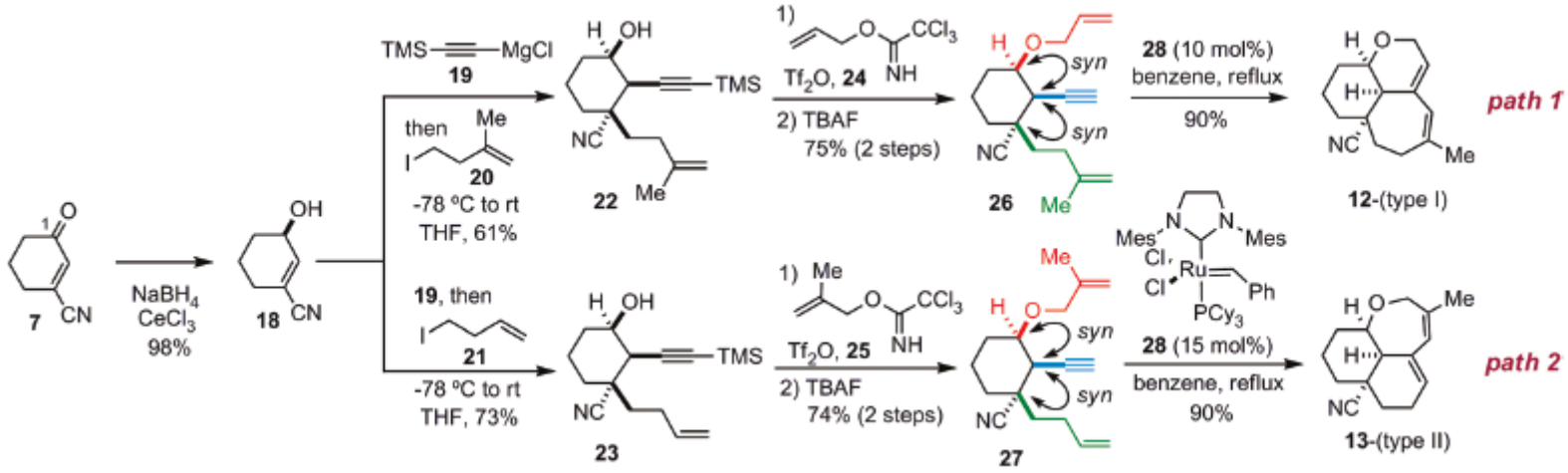


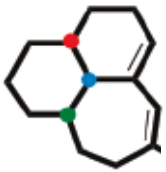
Design of a synthetic process (2)



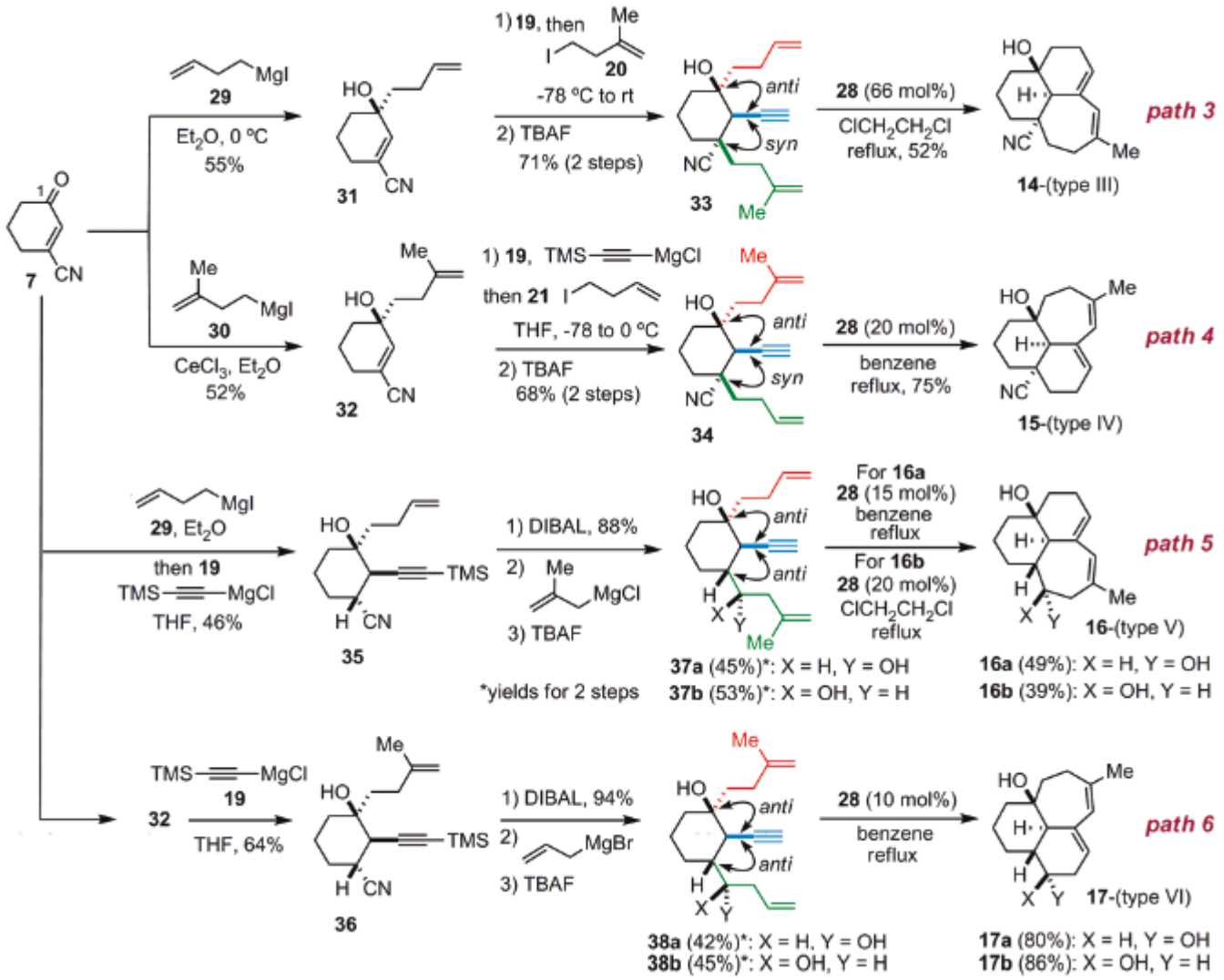


Systematic synthetic process (2)

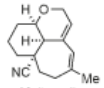
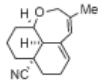
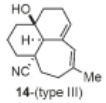
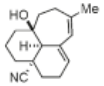
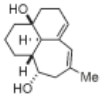
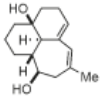
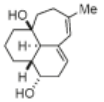
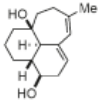


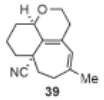
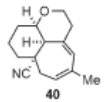
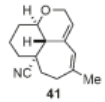
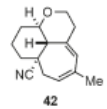
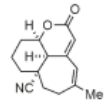
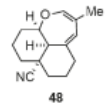
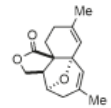


Systematic synthetic process (2)



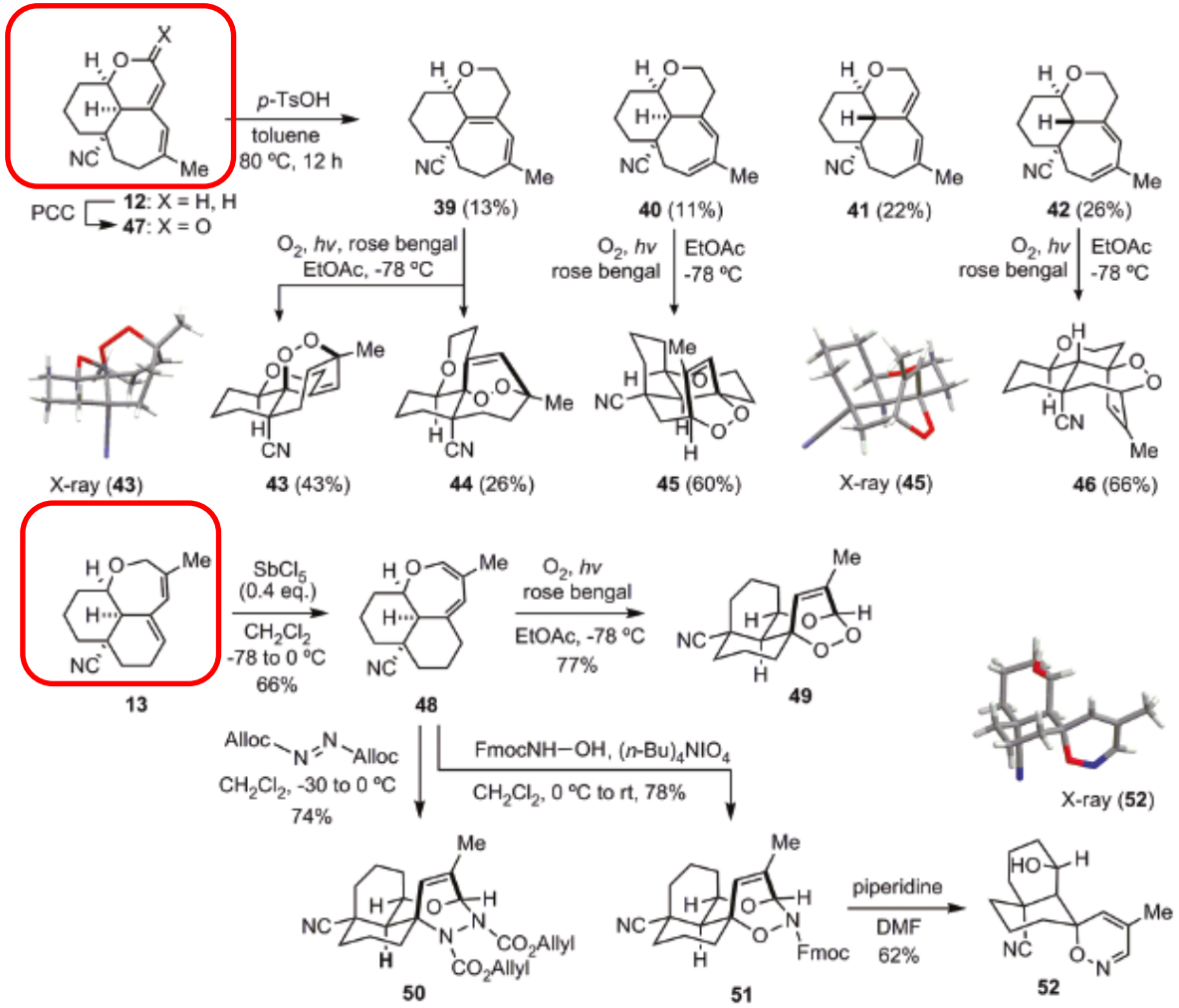
In-vitro anti-trypanosomal activities

entry	compound	IC_{50} (μg/mL) anti-trypanosomal activity	IC_{50} (μg/mL) cytotoxicity	selectivity index (SI)
1	 **12**-(type I)	0.55	59.9	109
2	 **13**-(type II)	1.1	>100	>90.9
3	 **14**-(type III)	2.42	76.5	31.7
4	 **15**-(type IV)	4.96	24.3	4.9
5	 **16a**-(type V)	1.92	75.9	39.5
6	 **16b**-(type V)	>12.5	ND[a]	(-)
7	 **17a**-(type VI)	>12.5	ND[a]	(-)
8	 **17b**-(type VI)	>12.5	ND[a]	(-)

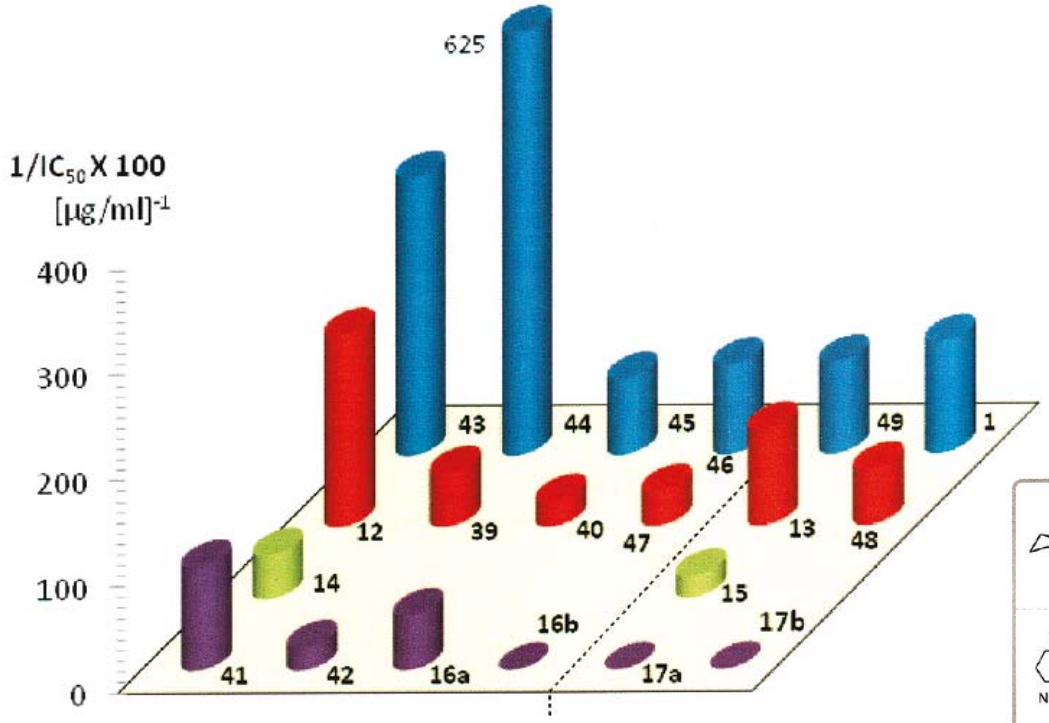
entry	compound	IC_{50} (μg/mL) anti-trypanosomal activity	IC_{50} (μg/mL) cytotoxicity	selectivity index (SI)
9	 **39**	1.98	45.4	22.9
10	 **40**	4.21	49.8	11.8
11	 **41**	1.02	40.0	39.2
12	 **42**	4.62	31.4	6.8
13	 **47**	3.0	3.73	1.2
14	 **48**	1.89	19.9	20
15	pentamidine[b]	0.00158	5.71	3600
16	suramin[b]	1.58	>100	>63
17	eflornithine[b]	2.27	>100	>44
18	 anthecularin (**2**)	10.1[c]		

[a] Culture of trypanosome ($2.0-2.5 \times 10^4$ trypanosomes/mL for GUTat 3.1 strain) was used. The cytotoxicities were evaluated with MRC-5 cells, a the selectivity index (SI) for trypanosomiasis was calculated as (IC_{50} for MRC-5)/(IC_{50} for *T. brucei brucei*). ND means "not determined". [b] Existing an trypanosomal drugs. [c] Reported in ref 19 against *T. brucei rhodesiense*.

SAR studies


p-TsOH
toluene
80 °C, 12 h
12: X = H, H
PCC
47: X = O
39 (13%)
40 (11%)
41 (22%)
42 (26%)
O2, hv, rose bengal
EtOAc, -78 °C
O2, hv
rose bengal
EtOAc
-78 °C
X-ray (43)
43 (43%)
44 (26%)
45 (60%)
X-ray (45)
46 (66%)
13
SbCl5
(0.4 eq.)
CH2Cl2
-78 to 0 °C
66%
48
O2, hv
rose bengal
EtOAc, -78 °C
77%
49
Alloc
N
N
Alloc
CH2Cl2, -30 to 0 °C
74%
FmocNH—OH, (n-Bu)4NIO4
CH2Cl2, 0 °C to rt, 78%
50
51
piperidine
DMF
62%
52
X-ray (52)

SAR studies



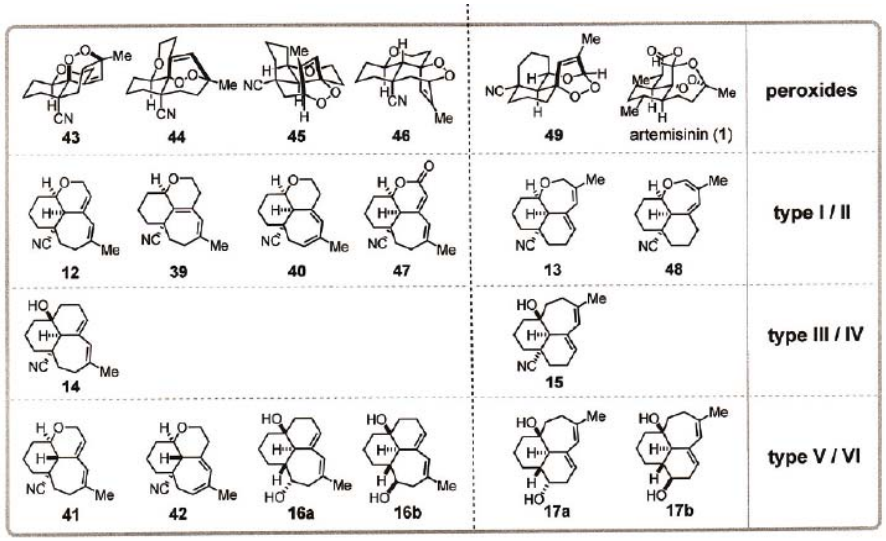
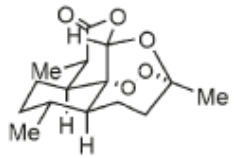
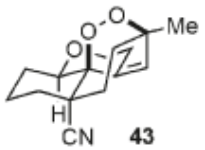
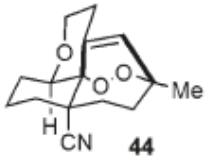
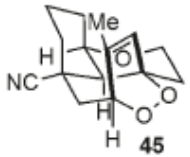
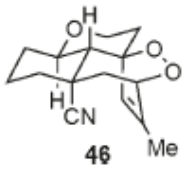
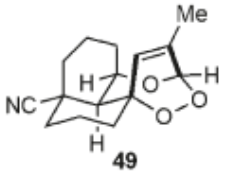
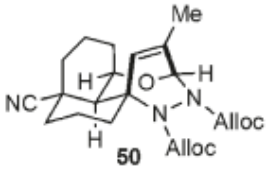
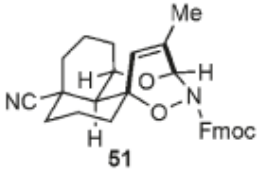
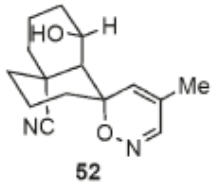


Figure 3. SAR study of synthetic sesquiterpene analogues for *in vitro* anti-trypanosomal activities. The dashed line divides types of the canonical scaffolds except for the lane of peroxides: left of the line are the potencies for type I, III, and V dienes; right of the line are those for type II, IV, and VI dienes.

SAR studies

entry	compound	IC_{50} (μg/mL) anti-trypanosomal activity	IC_{50} (μg/mL) cytotoxicity	selectivity index (SI)
1	 artemisinin (**1**)	0.94	45.2	48.1
2	 **43**	0.38	59.4	156
3	 **44**	0.16	59.9	374
4	 **45**	1.39	9.1	6.5
5	 **46**	1.18	17.1	14.5
6	 **49**	1.15	23.0	20
7	 **50**	4.88	ND[a]	
8	 **51**	3.68	>100	>27.2
9	 **52**	>12.5	ND[a]	

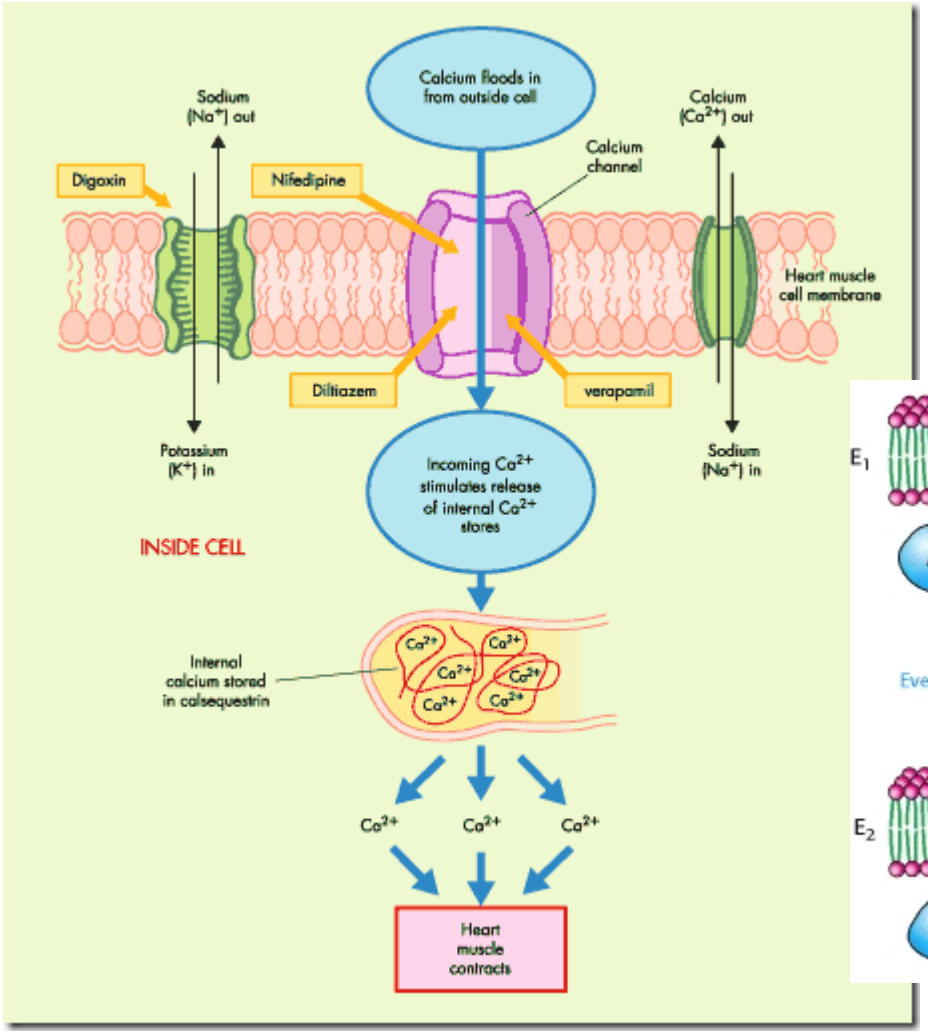
Conclusion

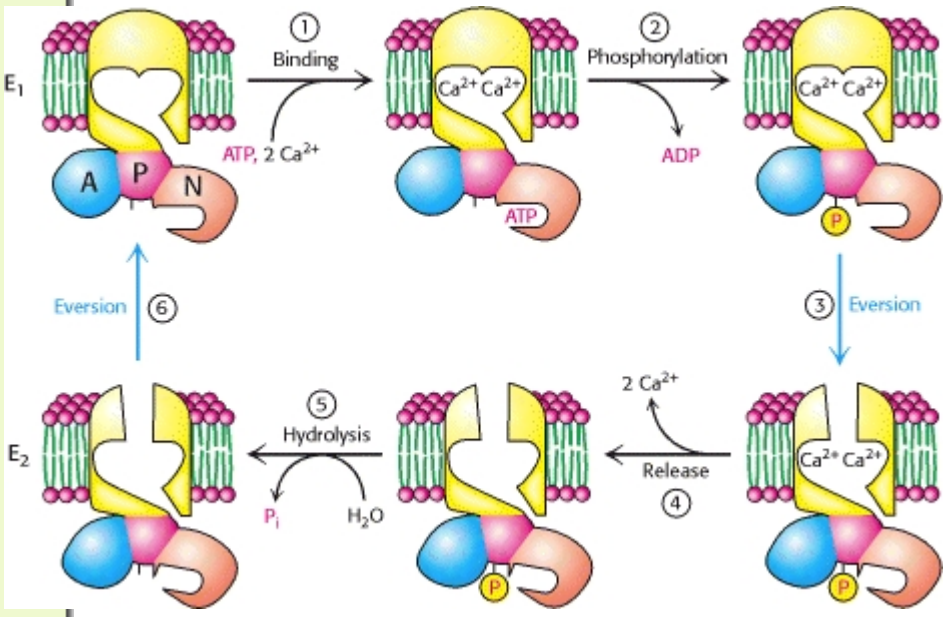
⇨ Developpment of a synthetic process that would produce collection of cyclic scaffolds exhibiting desirable biological activities

⇨ 6 types of scaffolds with systematic structural variations have been obtained from stereodivergent assembly of dienynes exploiting tandem ring closure metathesis

⇨ Screening of the compounds has been done to selected the best candidate for SAR studies. First modifications set on the best candidate chosen provided artemisin analogues that exhibited interesting activities even superior to those of artemisin and other approved drugs.

Some interesting Ca2+-ATPases inhibitors that exhibit anti-trypanosomal activities





Life cycle of parasite